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A STUDY OF THE SENSITIVITY OF HUMAN LEUKOCYTES TO TUBERCULIN AND OTHER BACTERIAL PRODUCTS BY THE BLATT, NANTZ, AND REHM TECHNIQUE

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IN 1947, Nantz and Blatt[12] published a description of a tissue culture type test for bacterial hypersensitivity of the leukocytes of human beings. The test which they described is similar to the one described earlier by Rich and Lewis.[15] Rich and Lewis used splenic cells and blood leukocytes from guinea pigs and were interested in sensitivity to tuberculin. Nantz and Blatt used human leukocytes and were interested mainly in sensitivity to products of microorganisms other than the tubercle bacillus. They state that theirs is a test of classical tuberculin type hypersensitivity.

In 1949, Blatt, Nantz and Rehm[7] published a description of what they called a modification of the original test of Nantz and Blatt which they claimed was simpler but gave the same results. Actually, the modification is an entirely different test. Their original test was a migration inhibition test but their modification is not. At any rate, it is by means of the "modification" that Blatt and his colleagues[1,2,4,5,6,9,13] have obtained the highly satisfactory results, which they reported, not only in the diagnosis of bacterial allergy but also in desensitizing the positive reactors with the bacterial filtrates to which the leukocytes of their patients reacted. A patient is not considered desensitized unless there is a remission of his symptoms and his leukocytes no longer give a "positive test" to the desensitizing filtrate.

Since this technique seemed to yield so much better results than the

This investigation was supported in part by grants from the Ohio Valley Allergy Society, the University of Kentucky Research Fund, and the U.S.P.H.S. (Grant No. H-2422).

From the Department of Bacteriology, University of Kentucky.

more cumbersome tissue culture techniques, we considered it worth while to compare it with one of the latter techniques, such as the one with which Hall and Scherago[10] obtained a differential cytotoxic effect on human leukocytes from tuberculous and nontuberculous individuals.

EXPERIMENTAL

I. Blatt, Nantz and Rehm Technique

Because we found it difficult to obtain the details of the technique from the published accounts of it, two of us spent some time in Dr. Blatt's laboratory observing the test as it was performed by his technicians. The test, hereafter to be referred to as the Blatt technique, was carried out as follows.

The principles of tissue culture technique as discussed by Cameron[8] and Parker[14] were followed throughout this study unless some variation was necessary in order to follow the technique employed in Dr. Blatt's laboratory (e.g., vaseline was sterilized in the autoclave; Ringer's solution was not that listed by these authors).

Solutions:

Ringer's Solution (formula furnished by Dr. Blatt)	
Sodium chloride (NaCl)	7.000 g
Calcium chloride ($CaCl_2$)	0.026 g
Potassium chloride (KCl)	0.350 g
Water (triple distilled)	1,000 ml
Calcium Ringer's Solution (formula furnished by Dr. Blatt)	
Sodium chloride (NaCl)	9.500 g
Calcium chloride ($CaCl_2$)	3.600 g
Potassium chloride (KCl)	0.200 g
Water (triple distilled)	1,000 ml

Bacterial Filtrates: These were Seitz-filtered trypticase soy broth (BBL) cultures of various strains of steptococci, staphylococci, and pneumococci, (prepared in Dr. Blatt's laboratory). For use in the tests these filtrates were diluted 1:1,000 in Ringer's solution.

Tuberculin: Old Tuberculin (Parke, Davis and Co.) diluted 1:1,000 in Ringer's solution was used in the tests.

Control Broths: Uninoculated trypticase soy broth (BBL) diluted 1:1,000 was used as a control for the tests using the culture filtrates. Glycerol broth having the same composition as that used in the production of the Old Tuberculin in a dilution of 1:100 was used as a control for the tests with Old Tuberculin.

Thrombin Solution: Bovine thrombin (Upjohn Co.) in a concentration of 200 units per milliliter was used in all of the tests.

A two per cent sodium citrate solution in triple-distilled water was used as the anticoagulant.

Equipment: The slide wells were made by placing Formica rings (kindly furnished by Dr. Blatt), previously sterilized in vaseline, on ordinary microscope slides that had been previously sterilized in the oven. Hand

drawn, uncalibrated, Pasteur pipettes were used to measure the reagents used in the tests. Aseptic conditions were maintained by preparing the tests in a tissue culture hood, surface sterilized with ultraviolet light.

Procedure: About four hours before the test was to be performed, approximately nine milliliters of blood were drawn aseptically by venipuncture, using a 20 gauge needle and a 10 ml syringe. The needle was removed and the blood expelled gently into a sterile test tube containing 1.5 ml of sodium citrate solution. The tube was inverted several times to mix the blood and the anticoagulant and, using a sterile five milliliter pipette, four milliliter aliquots were placed in two sterile 12 ml conical centrifuge tubes to sediment at room temperature. After three to four hours, three layers had formed in the tubes, an uppermost layer of plasma and platelets, an intermediate layer of leukocytes (the buffy coat), and a lower layer of erythrocytes. The plasma was then removed using a sterile capillary pipette, care being taken to leave a layer of plasma approximately one millimeter deep above the buffy coat. The final traces of plasma were then removed by carefully overlaying the buffy coat with the calcium Ringer's solution and then quickly removing the solution and plasma mixture. This washing was repeated, and then a third volume of the calcium Ringer's solution was added and allowed to remain in contact with the buffy coat.

When the buffy coat had coagulated sufficiently to allow it to be handled, but before clotting had extended into the erythrocyte layer (usually two to five minutes), it was gently freed from the tube wall with a platinum spatula and removed from the tube to a bath of the Ringer's solution. It was then freed of adhering erythrocytes by gentle scraping and kneading with platinum hooks. The buffy coat was then washed two to four times in fresh Ringer's solution and placed in a small sterile bottle containing three to four milliliters of the Ringer's solution and incubated at 37 C for one hour with occasional shaking.

The tests were made in slide wells prepared by placing Formica rings sterilized in vaseline on sterile microscope slides. These rings had been placed on glass rods and immersed in vaseline during sterilization, and when the vaseline had cooled sufficiently to allow handling the glass rod with its rings was removed from the vaseline and was allowed to drain. The rings were then removed from the rod one at a time with sterile forceps and placed on the sterile slides, two rings to each slide. Gentle pressure on each ring was used to assure its complete sealing to the slide. When the needed number of slides had been prepared they were surface sterilized by means of ultraviolet light.

After the buffy coat had incubated for one hour, the bottle was removed and shaken vigorously to suspend the leukocytes freed from the buffy coat during incubation. The tests were then prepared according to the protocol given in Table I. Three drops of bacterial filtrate, Old Tuber-

TABLE I. PROTOCOL FOR THE BLATT TECHNIQUE

Substance	Bacterial Filtrate Test	Bacterial Filtrate Control	Old Tuberculin Test	Old Tuberculin Control	Reagent Control
Bacterial filtrate	3 drops	—	—	—	—
Trypticase soy broth	—	3 drops	—	—	—
Old tuberculin	—	—	3 drops	—	—
Glycerol broth	—	—	—	3 drops	—
Ringer's solution	—	—	—	—	3 drops
Bovine thrombin	1 drop	1 drop	1 drop	1 drop	1 drop
Leukocyte suspension	1 drop	1 drop	1 drop	1 drop	1 drop

culin, control broths, or Ringer's solution, were added to the wells on appropriately labeled slides, followed by one drop of Bovine Thrombin solution and then by one drop of the leukocyte suspension in each. The slides were allowed to set for a few minutes and were then sealed by placing a cover glass on top of each Formica ring in such a manner as to avoid entrapping any air. Small (20 x 20 mm) cover glasses and sections cut from microscope slides were both tried. The latter were found to be somewhat more satisfactory because of less breakage and because their greater weight appeared to make a better seal. After sealing, the preparations were placed on a tray in a 37 C incubator for approximately twenty hours.

The preparations were examined using the 16 mm objective of the microscope and a light source with a green filter. Using an ocular grid, 100 cells were observed and the percentage of "necrotic" (morphologically altered) cells was determined. The average percentage obtained by the examination of the duplicate preparations was recorded as the per cent of "necrosis."

During our visits to Dr. Blatt's laboratory particular attention was paid to the method of reading and evaluating the tests. The interpretation of the results was based on the following criteria:

A "viable" leukocyte was one that had a relatively homogenous appearance, was spherical, and appeared to be surrounded by an entire peripheral membrane which had clearly defined interfaces. Such cells were recognized by us in preparations in Dr. Blatt's laboratory as well as in our own preparations.

A "necrotic" leukocyte was one in which the cytoplasm was more granular or vacuolated and frequently appeared less dense to light. Such a cell was frequently not spherical, and in many cases the "peripheral membrane" was ruptured or much less distinct than in the "viable" cells. Such cells were recognized by us in preparations in Dr. Blatt's laboratory and in our own preparations. The type of "necrotic" cell most frequently seen in our own preparations was one with a rather indistinct "peripheral membrane" and an irregular shape.

We evaluated our preparations on the basis of the percentage of mor-

phologically altered cells. A test was considered positive if the number of such cells in the test preparation exceeded by at least 10 per cent the number of such cells in the control preparations.

II. Hall and Scherago Tissue Culture Technique

This technique, hereafter to be referred to as the tissue culture technique, was carried out as follows:

In order to prevent injury to the leukocytes while the blood was being drawn and during subsequent handling, all surfaces with which the blood was to come in contact were rendered nonwettable, as suggested by Tullis and Rochow.[16] The needles were coated with Arquad C*, and the syringes, glass columns, and glass tubes with Dri Film SC-77**.

Freshly drawn venous blood was decalcified by passing it through a glass column containing Amberlite XE-132.† Three or four milliliters of the decalcified blood were centrifuged for ten to twenty minutes at 400 g. The plasma was removed and recentrifuged. The platelet-leukocyte layer (buffy coat) was washed and coagulated with Tyrode's solution and removed to a bath of Ringer's solution. It was then cut into small pieces, approximately one millimeter square, and placed in a bath of iced Ringer's solution until used.

The recentrifuged plasmas from several specimens were pooled, and the tissue culture media were prepared by adding appropriate volumes of the test reagents to 0.5 ml volumes of the pooled plasma and then adding enough Tyrode's solution to make the final volume one milliliter.

Four media were usually prepared for each test: Plasma-Tyrode's mixture (P-T), P-T plus glycerol broth, P-T plus Old Tuberculin, and P-T plus control filtrate. The glycerol broth‡ was uninoculated broth of the same composition as that which had been used in producing the Old Tuberculin. It was used at ten times the concentration of the Old Tuberculin. The Old Tuberculin§ was used in a final dilution of 1/100, 1/150, 1/200, depending upon the strength of the particular lot as determined by titration using the leukocytes of apparently healthy individuals. The control filtrate was a Seitz-filtered glycerol broth culture of *Mycobacterium avium* or of *Mycobacterium phlei*. The cultures used in the preparation of the control filtrates were obtained from the stock culture collection of the Department of Bacteriology, University of Kentucky.

Each tissue culture was prepared by placing a large drop of culture medium on the center of a cover glass and spreading it to cover an area 18 mm in diameter. Into this were placed four of the one mm square

*Arquad C—Armour and Company, Chicago, Illinois.
**Dri Film SC-77 (was 9977)—General Electric Co., Pittsfield, Mass.
†Amberlite XE-132—Rohm and Haas Co., Philadelphia, Penn. (No longer available, use IRC-50 and convert to pH 7.4).
‡Formula kindly supplied by Dr. Brigham of Parke, Davis, and Co., Detroit, Michigan.
§Old Tuberculin was Bio. 491, Parke, Davis & Co., Detroit, Michigan.

pieces of buffy coat so that they formed a small square in the center of the culture medium. A tissue culture slide* was appropriately labeled, lightly touched with vaseline in two places where contact would be made with the cover glass, and inverted over the culture. Gentle pressure was applied to stick the cover glass to the slide which was righted and the cover glass sealed in place with a mixture of ninety-five parts low melting point paraffin and five of vaseline. Duplicate cultures were prepared for each test condition. The slides were then placed in the 37 C incubator for eighteen to twenty-four hours.

Using the 16 mm objective of the microscope and an ocular micrometer, the amount of migration was determined by measuring the distance that the leukocytes had traveled from the edge of the piece of buffy coat. Two such measurements, at right angles to each other, were made for each piece. These were expressed in ocular micrometer units and the average of the sixteen measurements of the migration from the eight pieces of buffy coat exposed to each test condition was recorded as the migration figure for that specimen.

The degree of inhibition of migration was expressed as a ratio, the cytotoxic index, obtained by dividing the migration figure for P-T plus Old Tuberculin by the migration figure for P-T plus glycerol broth.

Experiment 1. Tuberculin Hypersensitivity

Since the Blatt technique, according to its authors,[12] is a test for tuberculin type hypersensitivity ("bacterial allergy") we had reason to expect that it would be most effective in the prototype of this type of allergy, hypersensitivity to tuberculin.

Using both the Blatt and the tissue culture techniques, we examined the leukocytes of fifty-three individuals, of whom twenty-five had active pulmonary tuberculosis and twenty-eight were nontuberculous. The latter group was composed of eleven individuals with inactive pulmonary tuberculosis, and seventeen with no history of tuberculosis (ten tuberculin skin test negative, and seven tuberculin skin test positive). The diagnosis of active pulmonary tuberculosis was based on clinical, bacteriologic, and roentgenologic findings. The classification of inactive tuberculosis was based on the presence of a stabilized roentgenologic picture. The results are given in Table II.

Of the twenty-five active cases, the leukocytes of twenty-two (or 88 per cent) were found to be sensitive to tuberculin by the tissue culture method; those of only four (or 16 per cent) by the Blatt technique.

Of the twenty-eight nontuberculous individuals, the leukocytes of three (or 10 per cent) were found to be sensitive to tuberculin by the tissue culture method, and those three were all individuals with inactive tuberculosis. With the Blatt technique, the leukocytes of five (or 18 per cent)

*A. H. Thomas Co., Philadelphia, Pa., No. 7047.

TABLE II. SENSITIVITY OF LEUKOCYTES FROM TUBERCULOUS AND NONTUBERCULOUS INDIVIDUALS TO OT

No. Individuals Tested (53)	Leukocyte Sensitivity to OT	
	Blatt Technique	Tissue Culture Technique
25 tuberculous	4 (16%)	22 (88%)
28 nontuberculous		
11 inactive TB	0	3
10 normal*, st-	3 (18%)	0 (10%)
7 normal*, st+	2	0

st—skin test.
*—no history of tuberculosis.

were found to be sensitive to tuberculin, and none of these were from the group with inactive tuberculosis.

It can be seen from these results that, on the basis of the Blatt technique, the incidence of leukocytic sensitivity was about the same among the nontuberculous individuals (18 per cent) as among the tuberculous (16 per cent).

An additional twenty-six individuals, twelve of whom had been diagnosed as tuberculous and fourteen as nontuberculous, were tested by the Blatt technique alone, and, again, it was impossible to differentiate between the two groups on the basis of this technique.

Experiment 2. Hypersensitivity to Bacterial Filtrates (other than tuberculin)

The failure of the Blatt technique to differentiate between the sensitivity to Old Tuberculin of the leukocytes of tuberculous and nontuberculous individuals appeared highly significant, since tuberculin hypersensitivity is considered to be the prototype of the delayed type of hypersensitivity. However, Blatt and his colleagues had made no mention in any of their publications of the use of their technique with the leukocytes of tuberculous individuals, although they had repeatedly stated in these publications that it would detect hypersensitivity of the tuberculin type caused by other microorganisms, such as streptococci, staphylococci, and pneumococci. We, therefore, conducted a series of tests using culture filtrates of such organisms.

We obtained from Dr. Blatt's laboratory fourteen bacterial filtrates which had been selected on the basis of their having frequently produced "positive results" in his laboratory. With these filtrates we tested the leukocytes from forty-seven blood samples obtained for us by two allergists* from allergic patients who had given positive skin reactions to bacterial allergens** as well as to others. The technique was carried out exactly as we observed it in Dr. Blatt's laboratory.

*We are indebted to Drs. Maurice Kaufman and Lloyd Mayer for furnishing these samples.

**Pneumococcus, "Strep Mix," *Staphylococcus aureus, Staphylococcus albus, Hemophilus influenzae, Klebsiella pneumoniae,* all from Hollister-Stier.

We found no significant differences in the reactions of the leukocytes from the forty-seven blood specimens to the fourteen filtrates and to the controls (uninoculated medium and Ringer's solution).

Experiment 3. Test for lysis of leukocytes using a tube technique

Blatt[2] states that "the percentage of cells which have been destroyed during their seventeen hours' exposure to an allergen represents the degree of the patient's sensitivity to that strain."

We therefore attempted to determine whether or not lysis of the leukocytes occurred in our Blatt technique test preparations. For this purpose we used a tube technique, patterned after the one described by Blatt (1951),* which made possible the accurate counting of the leukocytes before and after incubation. The technique which we used is as follows.

Cell suspensions, diluent, and filtrates were the same as those used in the Blatt technique. Small (75mm x 13mm) test tubes and standard white blood cell pipettes were cleaned in chromic acid cleaning solution and thoroughly rinsed in tap water, soaked overnight in double distilled water, and rinsed again in double distilled water.

To 0.6 ml of test solution, control broth, or diluent, in a small test tube, were added 0.2 ml of thrombin solution and 0.2 ml of cell suspension. The contents were gently mixed and placed in a 37 C incubator for approximately twenty hours. Counts were then made from each tube using standard white blood cell pipettes and Thoma type hemacytometers.

The same pipette and hemacytometer were used to sample all the tubes from one series of tests on one patient's cells. After having been used to sample one tube of a series, the pipette, before being used again, was rinsed with tap water and then twice with 95 per cent alcohol, after which it was dried by drawing air through it. The ratio of the number of cells present in a test substance to the number of cells present in the control substance was used as an index of the degree of lysis.

The leukocytes from twenty-one mental patients, thirteen of whom were tuberculous and eight nontuberculous, were tested. We found no appreciable difference in susceptibility to lysis between the leukocytes of the tuberculous and the nontuberculous individuals, in the presence of OT. This is contrary to what might have been expected from the Blatt et al reports.

Experiment 4. Viability of Leukocytes

Blatt[3] made an attempt to determine whether the leukocytes in his preparations were alive or dead after incubation for seventeen hours by staining them with neutral red. He concluded from his results that the majority of the cells in "negative" preparations and in control prepara-

*Lecture at the Graduate Instructional Course of the American College of Allergists, Chicago, Illinois.

tions not containing bacterial filtrate were viable while many of the cells in the "positive" preparations were dead.

In spite of these findings, a number of factors in the test, such as the pH of the solutions, the lack of nutritional material, and nonisotonic nature of the saline solutions which he used, suggested that human leukocytes might not remain alive for thirty-six hours as claimed by Blatt and Nantz[6] or even for the seventeen-hour incubation period used in the Blatt technique.

We therefore stained some preparations from our tube tests with neutral red. The method which we used is as follows.

A stock solution of neutral red was prepared by dissolving 250 mg of neutral red in 25 ml of double distilled water. From the stock solution a dilution of 1:10 was prepared as needed.

A cell suspension was prepared in Tyrode's solution from a buffy coat which had been removed from fresh blood after coagulation with Tyrode's solution and which had been washed in this solution. To one ml of the suspension in a test tube was added 0.09 ml of a 1:10 dilution of neutral red. The tube was placed in a 37 C water bath for twenty minutes. An aliquot of the cell suspension was placed in a hemacytometer and examined with the microscope using a magnification of 700 diameters. Many of the cells showed streaming cytoplasm and active pseudopodia. The cytoplasmic granules were stained red; only an occasional nucleus was stained red. A suspension of cells removed by Blatt's method and suspended in Blatt's modification of Ringer's solution was treated in a similar manner as the Tyrode's solution cell suspension. The cells were not motile and showed very few pseudopodia; most of the nuclei were stained red.

A sample of fresh blood was placed in two test tubes and allowed to settle for about three hours. The buffy coat was removed from each tube by coagulation with Tyrode's solution and was washed in Tyrode's solution. From each buffy coat two types of preparation were made and examined:

1. *Tissue Culture Preparation.*—This was prepared as described in the section on Hall and Scherago Tissue Culture Technique. At the end of six hours the preparation was examined microscopically. The leukocytes were found to be viable.

2. *Suspension preparation.*—A suspension was prepared by placing the unused portions of the buffy coat in about two ml of Tyrode's solution. Immediately thereafter a warm (37 C) slide preparation was examined with a phase microscope. The leukocytes showed streaming cytoplasm and were actively motile. A stained preparation was then made by adding 0.03 ml of a 3:10 dilution of the stock neutral red solution to one ml of cell suspension in a small test tube. The tube was placed in a 37 C water bath for twenty minutes. Aliquots from the suspension were placed on

a warm hemacytometer and examined immediately thereafter with a light microscope. Many of the cells were motile and their granules were stained red; only an occasional nucleus was stained red.

All these tests indicated that the leukocytes were viable in the tissue culture technique preparation (after six hours) in the leukocyte suspensions in Tyrode's solution and in the presence of a 3:10 dilution of the stock solution of neutral red, but not when exposed to the Blatt reagents.

Tube tests were then prepared as described in Experiment 3 from samples of blood from five individuals, three of whom were tuberculous and two nontuberculous. Five tubes were prepared for each sample of blood, one with OT 1:100, one with OT 1:1000, one with glycerol broth 1:10, one with glycerol broth 1:100, and one with Blatt's modification of Ringer's solution. The tubes were incubated for eighteen hours in the 37 C incubator. To each tube was then added 0.03 ml of a 3:10 dilution of neutral red and the tubes were placed in a 37 C water bath for twenty minutes. Immediately thereafter aliquots were placed in a warm hemacytometer and examined with a light microscope using a magnification of 700 diameters.

In practically all of the cells the usual neutral red staining reaction failed to occur. Instead, the cells had taken on a grey-greenish color. However, an occasional nucleus was stained red.

Since the typical staining reaction with neutral red occurs at a slightly alkaline reaction, we determined the pH of the test solutions used in the Blatt technique by means of a Beckman pH meter.

The pH in twenty-four of the tubes was found to be on the acid side. In the remaining tube (one containing glycerol broth) it was slightly alkaline (pH 7.05).

The tube tests were repeated using suspensions prepared from four samples of blood, but this time the pH of the preparation was adjusted to the slightly alkaline side by adding sufficient amounts of 0.15M K_2HPO_4 immediately before the neutral red stain was added. The pH in the twenty tubes ranged from 7.32 to 7.57. When the leukocytes from these preparations were examined the nuclei of nearly all the leukocytes from both the tuberculous and nontuberculous individuals were stained red. Apparently the cells in all these suspensions were dead. Since the environment in the tubes was essentially the same as that in the slide preparations, we believe that a high percentage of the leukocytes in those preparations were also dead.

COMMENT

Our failure to confirm the findings of Blatt and his colleagues naturally raises the question as to whether we carried out the technique as it is done in Dr. Blatt's laboratory. As stated earlier, it was difficult to obtain the details of the technique from the published accounts of it. To make sure that there would be no variation in the way in which we

performed the test from the way in which Dr. Blatt's technicians did it we visited his laboratory to learn the technique first hand. In addition, we communicated with Dr. Blatt and his technicians whenever we found it necessary to clarify some point.

One major difficulty which we encountered was Dr. Blatt's criterion for differentiating the leukocytes that were alive, "damaged," "necrotic," "dead," et cetera. The truth of the matter is that we could see little difference between the preparations from the leukocytes that were exposed to tuberculin and those that were not (the controls), regardless of whether the leukocytes were derived from tuberculous or nontuberculous individuals. Our results bear this out. As indicated in Table II, we obtained about the same percentage of sensitivity with the tuberculous individuals as with the nontuberculous. Nor were we any more successful when we tested the leukocytes from forty-seven patients that had been found to be skin sensitive to bacterial filtrates, even though we employed for the Blatt technique fourteen bacterial filtrates from Dr. Blatt's laboratory that had been selected on the basis of their having frequently "produced positive results" in his laboratory.

That there was no difference in susceptibility to tuberculin between the leukocytes from tuberculous individuals and those from nontuberculous individuals was demonstrated also by the results of the experiment (Experiment 3) in which we found the leukocytes of the former no more susceptible to lysis in the presence of OT than those of the latter.

Our results with supravital staining with neutral red (Experiment 4) were also at variance with those reported by Blatt. We found that the leukocytes prepared by the Blatt technique did not remain viable after they had been exposed to the Blatt reagents for eighteen hours. This was not surprising after we determined the pH's of the reagents and found them to be on the acid side.

Forman and Blatt,[9] after claiming that they have satisfied themselves that the method of "Blatt and Nantz" is reliable for the diagnosis of bacterial allergy and identifying the specific strains to which the individual is allergic, conclude that in intrinsic asthma the "Blatt-Nantz test"* furnishes "for the first time a specific desensitizing agent." They claim further that the reliability of the test has been repeatedly confirmed, but the only references they give in support of their claim are reports by Blatt and Nantz. No reports by any other workers are cited. Apparently no confirmation of the findings of Blatt and his co-workers by others has come to the attention of Forman and Blatt, nor to us. Furthermore, the basis for their claim that "This has been repeatedly confirmed" is "by the number of patients greatly improved or rendered free of their symptoms

*Although they use the term "Blatt-Nantz test" throughout their paper, it is presumed that Forman and Blatt used the Blatt, Nantz and Rehm (1949) technique, and not the tissue culture method of Nantz and Blatt (1947).

by the use of carefully graduated injections of dilutions of the filtrates from the offending organisms. When this occurs, the leukocytes of these patients are no longer susceptible to the filtrates which at the beginning consistently damaged them."

Millman and Millman[11] tried to obtain living leukocytes by the Blatt technique with the idea of attempting to repeat the Blatt et al studies. The Millmans concluded that "Studies using this technique were unsuccessful because: (1) We were unable to obtain a sufficient number of leukocytes. This was probably due to the cumbersome method of obtaining the leukocytes. The buffy layer was difficult to remove intact, and carried with it numerous erythrocytes. (2) It has been difficult to determine by this method which leukocytes were alive and which were dead."

SUMMARY

Leukocytes from seventy-nine individuals, thirty-seven of whom were known to be tuberculous and forty-two nontuberculous, were tested for sensitivity to Old Tuberculin by the method of Blatt, Nantz, and Rehm.[7] It was impossible to differentiate between the leukocytes of the two groups by this method.

A tube test modification of the Blatt technique also failed to differentiate the leukocytes of the tuberculous from those of the nontuberculous individuals.

Leukocytes from forty-seven individuals, suspected of having bacterial allergy, were tested for sensitivity to 14 bacterial filtrates by the Blatt technique. No differences could be detected in the reactions of the leukocytes from these individuals.

Attempts to stain the leukocytes in the preparations made by the Blatt technique were unsuccessful unless the pH was adjusted to the slightly alkaline range. When the pH was so adjusted, nearly all the nuclei stained red in preparations that had been incubated at 37 C for approximately eighteen hours. Hence, it is very doubtful that the leukocytes remain viable for thirty-six hours as claimed by Blatt.

We have been unable to confirm the claims of Blatt et al for their test for bacterial allergy.

REFERENCES

1. Blatt, H.: The role of bacterial allergy in the rheumatoid state, Ann. Allergy, 9:930 (May-June) 1951.
2. Blatt, H.: The identification of specific allergens in bacterial allergy and their use in desensitization. Ann. Allergy, 10:53 (Jan.-Feb.) 1952.
3. Blatt, H.: Personal communication, 1953.
4. Blatt, H., and Nantz, F. A.: Asthma due to bacterial allergy: identified by tissue culture and treated by desensitization. Ohio State M. J., 45:40 (Jan.) 1949.
5. Blatt, H., and Nantz, F. A.: Sinusitis due to bacterial allergy: identified by tissue culture and treated by desensitization. Ohio State M. J., 48:319 (Apr.) 1950.
6. Blatt, H., and Nantz, F. A.: Further studies on the use of tissue culture of blood leukocytes in the clinical evaluation of bacterial hypersensitivity of the tuberculin type. Ann. Allergy, 8:622 (Sept.-Oct.) 1950.

7. Blatt, H., Nantz, F. A., and Rehm, Jeanne M.: An improved tissue culture technique adaptable to clinical testing for bacterial hypersensitivity of the tuberculin type. Ann. Allergy, 7:170 (Mar.-Apr.) 1949.
8. Cameron, G.: Tissue Culture Technique. New York: Academic Press, Inc., 1950.
9. Forman, J., and Blatt, H.: Bacterial allergy as a cause of so-called intrinsic asthma in the elderly patient, J. Am. Geriat. Soc., 2:662-665 (Oct.) 1954.
10. Hall, H. E., and Scherago, M.: Sensitivity of human leukocytes from tubercular and non-tubercular individuals. Bact. Proc., 1955, p. 99.
11. Millman, S., and Millman, M.: Preliminary studies on an *in vitro* test for the detection of bacterial allergies. The Letters of the International Correspondence Society of Allergists. Series XVIII; p. 70-76, 1955.
12. Nantz, F. A., and Blatt, H.: The application of a tissue culture technique in the clinical evaluation of bacterial hypersensitivity. Ann. Allergy, 5:554 (Nov.-Dec.) 1947.
13. Nantz, F. A., and Blatt, H.: Bacterial hypersensitivity; its diagnosis and treatment. Eye, Ear, Nose & Throat Monthly, 28:529 (Nov.) 1949.
14. Parker, R. C.: Methods of Tissue Culture. New York: Paul B. Hoeber, Inc., 1950.
15. Rich, A. R., and Lewis, M. R.: The nature of allergy in tuberculosis as revealed by tissue culture studies. Bull. Johns Hopkins Hosp., 50:115, 1932.
16. Tullis, J. L., and Rochow, E. G.: Nonwettable surfaces. Blood, 7:850, 1952.

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SECTION ON ALLERGY, AMERICAN MEDICAL ASSOCIATION

At the 1957 meeting of the American Medical Association, the Section of Allergy will meet on Wednesday afternoon, June 5, at 2 o'clock, at the New York Coliseum in the third floor meeting room. The co-chairmen are Drs. Carl E. Arbesman, Buffalo, New York, and Ethan Allan Brown, Boston, Massachusetts. The secretary is Dr. Clarence J. Bernstein, Orlando, Florida. The possibility of obtaining a section is based in part on the attendance at the session. It is hoped that all College members will register for the session on allergy and attend.

CLINICAL ASSISTANT

Openings for clinical assistants are available in the Allergy Clinic of The Brooklyn Jewish Hospital. Members of the clinic staff attend clinical conferences, seminars, and literature review meetings. The opportunities for self-development in the field of practical allergy and experimental investigation are abundant. There will be an opportunity for advancement to the In-Patient-Service. Those interested are requested to contact Dr. Max Grolnick, Attending-In-Allergy, The Brooklyn Jewish Hospital.

RESIDENCY IN ALLERGY

The Allergy Division of The Jewish Hospital of Brooklyn will have an opening for a Resident-In-Allergy beginning July 1, 1957. The opportunities for development are numerous. The department is an active one, affording a wide scope of both detailed clinical study and basic experimental investigation. Upon completion of the residency, an in-patient staff appointment will be offered, if the obligations of the position can be fulfilled. Those interested are requested to contact Dr. Max Grolnick, Attending-In-Allergy, The Brooklyn Jewish Hospital.

ALLERGIC DERMATITIS PRODUCED BY PATHOGENIC AND SAPROPHYTIC FUNGI

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ALL the different phases of allergic skin diseases can be produced by fungi which are also excellent tools for the experimental production of allergic skin diseases. Data derived from these studies can be applied to other diseases. Therefore, a comprehension of fungous allergy aids not only in the understanding of dermatologic allergy, but provides a knowledge of basic allergic principles as well.

The dermatophytes and the airborne saprophytic molds, acting as allergens, will be the subject of this paper.

DERMATOPHYTIDS

Dermatophytid is the name given to the group of skin diseases resulting from allergic reaction to fungous infection involving the keratin of hair, skin or nail (dermatophytosis).

The following minimal criteria must be fulfilled in order to establish a diagnosis of dermatophytid: (1) a proven focus of dermatophytosis; (2) positive skin tests to trichophytin; (3) precipitation of the dermatophytid due to blood-borne fungi or fungous products released by activation of the dermatophytosis, or overtreatment of the dermatophytosis; (4) absence of fungi in the dermatophytid lesions; and (5) clearing of the dermatophytid after the dermatophytosis has been eradicated.

Further elaboration on the criterion of a positive skin test to trichophytin is necessary. The antigen used is the group-specific antigen; that is, the antigen that is in common with all the species found in the three genera of the dermatophytes and also in the mold *penicillium*. In a few instances, it may be necessary to test with the species-specific antigen acquired from the autogenous fungus.

There are at least three types of skin reactions that may follow the intradermal injection of trichophytin: (1) the immediate wheal (urticarial type) appearing in fifteen to thirty minutes; (2) the papule (tuberculin type) appearing in twenty-four to forty-eight hours; and (3) the plaque (eczematoid type) appearing in one week.

In the process of sensitization, the time element is reversed in the establishment of these three basic types of skin reactions, the first to occur being the delayed eczematoid response at one week. This reaction appears only on the initial testing with trichophytin, and persists for two to three weeks. If these patients are retested, only the twenty-four to forty-eight-hour papular reaction is found.[1]

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On the other hand, this papular response may disappear, or may be replaced by the wheal reaction, when a constant supply of fungous antigen is maintained, either by injection of trichophytin or by chronic dermatophytosis.[2] This may explain why the majority of patients with the chronic, recalcitrant *Trichophyton rubrum* infection of palms and soles will have an immediate wheal reaction to trichophytin.

In other diseases, the importance of the time element or of repeated injections in changing the delayed papular response to the wheal is noted.[3,4] For example, in the early stages of trichinosis, the skin response to the trichinella extract is a papule appearing at forty-eight hours. Later, as the disease becomes chronic, the specific skin test is a fifteen-minute wheal.

Various investigators have proposed the following types of dermatophytids: (1) disseminated papular lesions;[5] (2) vesicular lesions of the hands;[6,7] (3) erysipelas-like dermatophytid of the lower extremities (sometimes eventuating in chronic lymphedema);[8-10] (4) migrating thrombophlebitis and thromboangiitis obliterans;[11-13] (5) urticaria (often associated with asthma and vasomotor rhinitis);[14-16] and (6) miscellaneous group (erythema multiforme, erythema nodosum, exfoliative dermatitis, eczematous lesions simulating pityriasis rosea, and erythema annulare centrifugum).[17-20]

DISSEMINATED PAPULAR LESIONS

The widespread follicular papular "ids" are found chiefly in children. The disease is self-limited and disappears without treatment in a week. It is associated with the inflammatory type of ringworm involving the hair (kerion).

When there is fungous infection of the hair, a permanent immunity is established eventually. Therefore, the reinfection rate in a given epidemic of ringworm of the scalp is only about one case in four hundred.[21] In a type of fungous disease of hair acquired from animals, known as "barn itch," the infection is acquired only once, even though there is constant exposure to infected cattle.[22] Kligman has shown that it is almost impossible experimentally to produce ringworm of the scalp in patients who have had this disease previously.[23] This is in marked contrast to ringworm infection of skin and nail. Certainly, little or no immunity is found in tinea pedis.

VESICULO-PAPULAR DERMATOPHYTID OF THE HANDS

This is the most frequently observed type of dermatophytid. The small lesions are symmetrically located on the hands. They appear initially some two weeks after the activation of tinea pedis and twenty-four to forty-eight hours after penicillin therapy in susceptible individuals. This type of "id" is seldom seen before puberty, since tinea pedis, the usual sensitizer, is a rarity in children. It is of interest that penicillin reactions are very uncommon in children.

ERYSIPELAS-LIKE DERMATOPHYTID

This type of dermatophytid is characterized by recurrent plaques of

erythema located on the lower extremities, and there are associated constitutional symptoms. Although the course is self-limited, the duration is variable, lasting from a few days up to two weeks. Repeated episodes of this disease will eventuate in chronic lymphedema, followed by the hyperpigmented verrucous lesions pathognomonic of lymphatic disease. There is frequently a background of venous stasis with its resultant hyperkeratotic, macerated, intertriginous tinea pedis. Effective treatment of the tinea pedis will prevent recurrence of the disease.

Thompson[12] noted a more persistent reaction to trichophytin when it was injected at the site of lymph statis or edema. Naide[24] suggested that due to trapping of the antigen by venous disease, there might have been more time for the antigen to act. In any event, the importance of time and a constant supply of antigen in the process of sensitization is well demonstrated here. As would be expected, the skin test reaction is of the wheal type. Trichophytin injected into the site of the disease can reproduce the entire plaque of dermatitis within fifteen to twenty minutes.

MIGRATING THROMBOPHLEBITIS

Although only provocative studies have been presented associating fungous allergy with thromboangiitis obliterans, it is definitely established that superficial thrombophlebitis of the leg can follow activation of tinea pedis. Extreme hypersensitivity to trichophytin in primary idiopathic recurrent thrombophlebitis has been noted.[25] Routine skin testing has produced necrosis, ulceration and scarring at the test site. A positive skin test has been obtained to trichophytin diluted 1:1,000,000. Although the skin test cannot mimic the disease, since the shock organ is the vein, positive skin tests have been followed by thrombophlebitis in the vicinity of the test area.

MISCELLANEOUS GROUP

It is in the miscellaneous group of dermatophytids (urticaria, erythema multiforme, erythema nodosum, and erythema annulare centrifugum) that it can be demonstrated so well that the trichophytin skin test simulates the dermatophytid. For example, the skin test is of the wheal type in urticarial dermatophytids and may precipitate an acute episode of asthma or rhinitis. In erythema annulare centrifugum, the trichophytin test site shows a typical delayed papule in forty-eight hours, both within and adjacent to the lesion. The skin test reaction outside of the lesion clears centrally, while spreading peripherally, to form at one week a small lesion simulating erythema annulare centrifugum. Concomitantly, there is fading of the reaction within the lesion.[20] Thus, two things can be noted. The skin test not only mimics the "id" in question, both in its morphology and in its evolution, but a specific altered allergic reaction is produced locally in the resolved central area of the lesion.

Requiring further amplification is the criterion that the dermatophytid must clear after the dermatophytosis has been eradicated. Anti-fungal foot

care must be carried out daily to prevent recurrences. Superficial onychomycosis is frequently present. This type of toenail infeetion is caused by *Trichophyton mentagrophytes*, the fungus most frequently involved in the causation of dermatophytids. It is effectively controlled by daily use of a nail brush, followed by the application of tincture of iodine U.S.P. If this nail focus is not treated, the dermatophytid may persist or recur.

In the investigation of the unusual or unrecognized dermatophytid, it may be necessary to reproduce experimentally a dermatophytid, which can be accomplished by the following method.

A moist cotton pad inoculated with the suspected fungus obtained from culture is placed in the fourth interdigital space, and the adjacent toes are held together by a piece of tape. By this method, an experimental intertriginous tinea pedis can be produced. This active infection should precipitate the dermatophytid in question, and the eradication of this experimental focus should cause the dermatophytid to disappear.

Finally, it should be emphasized that the skin test must mimic clinically, chronologically, and histopathologically the dermatophytid in question.

SAPROPHYTIC MOLDS

In the past decade, increasing emphasis has been placed on the importance of inhalants in the production and aggravation of atopic diseases.[26-31] Among these, the nonpathogenic, airborne fungi are admirably suited for the study and understanding of the role of these inhalants in the causation of atopic dermatitis.[32]

Our experience in this field has been applied chiefly to a common dermatologic problem, eczematous dermatitis of the hands (excluding industrial or contact dermatitis). These chronic hand cases occur chiefly in women, over 50 per cent of whom have an atopic background. Even a higher percentage of these patients will be found to be atopic if the finer anatomic and physiologic stigmata of atopy are looked for or demonstrated. These have been well described by Lobitz,[33] and include infra-orbital pleat, white dermographism, delayed blanch reaction to intradermal acetylcholine, increased palmar markings, and a characteristic reaction to selected patch tests (*loc cit.*).

DIAGNOSIS

Seasonal history is of prime importance in diagnosis. Because of this, those cases produced by the seasonal pollens are the easiest to prove. It is difficult to produce incontrovertible evidence of the role of other inhalant allergens, such as wool, dust and feathers, in the etiology of eczema. In those cases due to saprophytic molds, there may be a definite seasonal history. The dermatitis may begin in the spring or fall, and clear late in the winter when the ground is covered with snow. With complete snow cover, there is a sharp drop in the total air mold count, and then with thaw there is a rise once again, which reaches a peak in the fall when the ground is covered with decaying vegetation. Later the dermatitis will become per-

sistent and chronic, with exacerbations during the spring, summer and fall, and with partial remission during the winter months. This chronicity is caused by secondary factors such as overtreatment and superimposed bacterial eczema.

In order to evaluate precisely the relationship between the total mold count and the course of the dermatitis, it is necessary to do daily mold counts. This is best accomplished by exposing to the air for twelve minutes Petri dishes 9 cm in diameter containing Sabouraud's agar. By this means, correlation between the mold count and the course of the dermatitis will explain some of the exacerbations and remissions of the disease. In addition to the seasonal variations in the mold count, it will be noted that there is a drop in the mold count after a rainstorm. If this is followed by three or four warm and sunny days, the mold count will rise sharply.

Mold counts taken at home as well as at the place of work may be necessary to explain another factor in the lack of seasonal history, the onset of the dermatitis after moving into an old dwelling, or the clearing of the disease when changing residence or occupation. In general, *Penicillium* and *Aspergillus* predominate in the air indoors, while *Alternaria* and *Cladosporium* predominate in the air outside.[34] Our studies strongly indicate the necessity of studying the molds in the patient's home environment. Pronounced variations from the outdoor air are found, and one species of mold may predominate consistently.

Other factors in the history that may suggest mold sensitivity are as follows: (1) sensitivity to penicillin, of which the most significant reaction in this regard is the twenty-four to forty-eight-hour erythematous vesicular type; (2) flare of the dermatitis after ingestion of mushrooms or foods containing fungus, such as Roquefort and Camembert cheese, soy sauce, et cetera; and (3) certain occupations, such as gardening with tomatoes (the responsible mold being Cladosporium),[35,36] farming, and working in damp environments.

SKIN TESTS

The next phase in the diagnosis is the performing and interpretation of skin tests. In the study of atopic dermatitis due to inhalants, intradermal skin tests and patch tests may verify a clinical impression, or point to an allergen which could not be detected by history. Scratch tests are of little value except as an initial precautionary procedure.

Intradermal Skin Tests

1. Concentration of Extracts:

The average concentrations of the more commonly used extracts are as follows: dust 1:10; trees 100 PNU/cc (composite of ash, birch, hickory, oak, and poplar); timothy 100 PNU/cc; ragweed 100 PNU/cc; molds 1000 PNU/cc (composite of *Mucor, Helminthosporium, Alternaria, Penicillium, Trichoderma, Aspergillus niger, Aspergillus fumigatus, Clado-*

sporium, and *Cephalothecium*); feathers 1000 PNU/cc; wool 1000 PNU/cc; *Staphylococcus ambotoxoid*® 1:20; and Dermatomycin® 1:30.

2. Testing Amounts:

It is necessary to inject 1/10 cc of the allergenic extract intradermally in order to demonstrate the delayed twenty-four to forty-eight-hour skin reactions. With proper concentration and interpretation of the skin tests, false positive reactions have not been a problem. In testing several thousand patients, only two constitutional reactions have occurred, one to trichophytin, and the other to tree pollens. When the history suggests the presence of an immediate wheal type of allergy, such as hay fever or asthma, scratch tests may be employed initially, or the accepted lesser amounts (.01 to .02 cc) of the suspected allergen may be injected intradermally.

3. Interpretation of Skin Test Reactions:

As in testing with trichophytin, three types of reactions have been noted: wheal, papule, and plaque. In addition, a four to six-hour edematous reaction may occur.

(A) The Immediate Wheal Reaction.—There are several factors that must be considered in the interpretation of the wheal reaction in the study of atopic dermatitis.

(I) A positive reaction may be related to past, present, or future immediate wheal types of allergy (asthma, hay fever, urticaria) and have no relationship at all to the atopic dermatitis. Because of this, early in our studies, when the ideal criteria for the diagnosis of inhalants in atopic dermatitis were established, wheal reactions were not used as confirmatory or suggestive evidence to indict a suspected allergen.[35]

(II) A positive reaction may utilize the antigen completely, and therefore no antigenic extract remains to produce the papule at forty-eight hours. Marcussen[36] demonstrated this by doing passive transfer studies in patients with a normal papular reaction to trichophytin. On injecting trichophytin into the prepared passive transfer site, only a wheal occurred; but when trichophytin was reinjected into the same site after the disappearance of the wheal, a papule appeared at forty-eight hours.

Since the tuberculin type of reaction may represent the early stage and the wheal type of reaction the late stage in the development of the sensitization process, it could be assumed that if the immediate wheal type of allergies are present, then the tuberculin type of sensitivities are also present. These are either masked or not demonstrated by intradermal skin tests.

(III) A positive wheal reaction without a subsequent delayed papular reaction may be associated within twelve to forty-eight hours with a flare of the original dermatitis or precipitate new lesions. If this can be demonstrated consistently, then this type of wheal reaction is of etiologic significance. Experimentally this has been demonstrated.[30] In a patient with a

positive wheal reaction to Alternaria, there was a flare of the dermatitis twenty-four hours after nasobronchial instillation of this allergen.

(B) The Four- to Six-Hour Edematous Reaction.—It is easy to miss this four- to six-hour reaction, as it does not appear during the time that the patient is being observed immediately following skin testing, and is gone when the skin test sites are re-examined two days later.

This type of reaction is characterized by a large tender swelling 2 cm or more in diameter surrounded by a large flare, appearing four to six hours after skin testing, and persisting for about twelve hours. This has been noted after repeated injections of trichophytin[2] and on routine skin testing with inhalants and especially with foods.

In a study of a case of vernal conjunctivitis, the four to six hour edematous response was obtained to the composite tree antigens. On re-testing to the separate tree pollens, immediate wheal reactions appeared within minutes and were associated with a constitutional reaction.

(C) The Twenty-four to Forty-eight Hour Papular Reaction.—Using the method of testing described in this paper, less than 5 mm papules may be noted at twenty-four hours in a few cases. These reactions fade by forty-eight hours, the time at which the specific papular reaction is at its height.

The following factors must be considered when using this type of skin test as an aid in diagnosis:

(I) The capacity to produce a papular response may persist for years or indefinitely and bear no relationship to the present allergic skin disease.

(II) The positive reaction may be related to allergic diseases other than those of the skin. Many cases of chronic nasal allergy and vernal conjunctivitis are of the delayed papular type of allergy.[37-39] Following the intradermal skin tests, the nasal symptoms do not flare within fifteen to twenty minutes, but within twenty-four to forty-eight hours, and these cases may be associated with the delayed type of skin test reactions.

(III) A positive skin test to molds may be related to chronic onychomycosis. Many nonpathogenic fungi can be isolated from thickened distorted toenails. Delayed reactions to dust and feathers may also be a reflection of chronic onychomycosis, since molds are always present in dust and may be an activating factor in feather antigenicity.

(IV) The positive reaction may be associated with a concomitant flare of the dermatitis. This combination of findings is the strongest aid in diagnosis that can be obtained by means of skin testing. If, in addition, there is initially a seasonal incidence of the dermatitis that agrees with these positive skin tests, then proper desensitization therapy will have its greatest effectiveness. Unfortunately, these ideal criteria for the diagnosis of eczematous dermatitis are not found in a majority of cases. Diagnosis will frequently depend on history, and, with experience, successful desensitization therapy can be accomplished in patients with negative skin tests.

(D) The One Week Eczematous Reaction.—On occasion no reaction is noted until five to seven days. At that time a large eczematoid plaque appears and persists for one to two weeks. Invariably it is associated with a flare of the dermatitis and certainly is of etiologic significance.

Patch Tests

As suggested by Cooke,[40] much information can be obtained through the use of patch tests. In the atopic individual, two types of patch test reactions are noted:

1. The Atopic Patch Test Reaction:

The best description of this is by Albert and Walzer.[41] It has been produced by patch testing with feathers, silk, ragweed, and certain foods. It is characterized by closely aggregated, discrete, pinpoint sized vesicles and occasionally pustules. There is no exudation and crusting. Erythema is minimal and is localized to the patch test site. The reaction reaches its height at four to five days. This type of reaction has been noted in atopic individuals with or without atopic dermatitis.[42] If dermatitis is present, a positive test is not associated with a flare of the dermatitis, and the spontaneous flare phenomenon is absent.

A very similar reaction is noted in testing to nickel.[43] Of interest is Vollmer's[44] description of a somewhat different type of reaction which he referred to as pseudoreactions to the tuberculin patch test. These occurred almost exclusively in persons with a personal or family history of allergy. The value of this atopic patch test type of reaction is that it serves to identify the atopic individual just as much as a past history or family history of asthma, hay fever, and eczema.

2. The Allergic Patch Test Reaction:

The allergic patch test reaction has been noted in testing to molds,[45] defatted pollen protein of grass,[46] ragweed,[47] feathers,[48] and dander,[49] among other allergens. This well known allergic reaction differs markedly from the atopic patch test reaction, in that it is characterized by erythema, vesiculation, exudation and crusting. Furthermore, the reaction may spread beyond the patch test site and may be associated with a flare of the dermatitis. In addition, the spontaneous flare phenomenon may be observed.

This specific type of reaction can detect allergens missed by intradermal testing in those cases where the antigen was utilized completely in the immediate wheal response, leaving none to evoke the delayed papular reaction.

The method used by Vollmer[50] in preparing the tuberculin patch test can be utilized in preparing patch tests for the various inhalant protein allergens.

In partial answer to the question of whether these antigens act as contactants or inhalants, it is worth while to recall that following contact dermatitis to many agents (sulfa, antihistamines, quinine, poison ivy,

dyes), then the eczematous dermatitis can be elicited by ingestion, injection, or inhalation of these substances.

TREATMENT

In treatment, it is essential to give detailed instructions for the avoidance of molds. All dust contains saprophytic fungi, so a dust-free environment should be maintained as much as possible. Foam rubber pillows and plastic coverings on upholstered furniture and mattresses will not only reduce dust, but feather pillows and mattresses are an important source of fungi in themselves, the predominant fungus being *Rhizopus*.[51]

The efficacy of such measures as dehumidification, and removal of wood piles, mildewed clothing, and decaying vegetable matter can be proved by before and after mold counts. Likewise, ingestion of mushrooms and foods containing fungi should be avoided.

Desensitization is accomplished by means of extremely dilute antigens given in relatively fixed amounts, which are usually self-administered.[35,52,53] The amount of antigen used is that amount which, when injected intradermally, does not produce a local reaction or a systemic flare. One-tenth of a cubic centimeter of the chosen extract is given subcutaneously twice weekly until the dermatitis has been clear for several months; after that, the interval between the injections may be increased until finally a "booster shot" is given every three or four weeks. The average dilution of the extract is 1:100,000, or 1 protein nitrogen unit per cc.

There is no response to the desensitization treatment for six to eight weeks. At this time, itching begins to decrease, and later the dermatitis begins to clear. It will be necessary to continue the desensitization therapy for a year or longer.

A simple method for observing whether the correct dilution of the extract is being given is to have the patient record each injection on a calendar. If the dermatitis flares the day after the injection, the extract should be diluted. Later, as the dermatitis begins to respond to treatment, an exacerbation of the dermatitis just before the next treatment signifies that the unitage should be increased.

The types of molds used in the desensitization therapy will depend on the predominant air molds in the locale of the patient, or those found in the home. Over 95 per cent of these fungi will be found in nine or ten groups of fungi,[32] the most consistent of which are yeasts, *Alternaria*, *Cladosporium*, *Aspergillus*, *Penicillium*, *Pullularia*, and *Mycelia sterila*. If this information is not available, then it is best to treat with a combination of dust and molds. The addition of dust will supply many of the important fungi, some of which will be duplicated in the mold mixture. Therefore, it will be necessary to use weaker concentrations, such as dust 1:1,000,000 or molds 1/10 protein nitrogen unit per cc.

Because of the constant presence of superimposed bacterial eczema, we agree with Epstein[54] that staphylococcal antigen should be added to all ex-

tracts employed in the desensitization of eczematous dermatitis. This is effectively supplied by adding Staphylococcus ambotoxoid® 1:100,000.

Because of the slow response to desensitization therapy, topical dermatologic treatment is necessary to give more immediate relief. Dermatologic therapy alone can very often clear the dermatitis, but recurrence is common. With combined topical dermatologic therapy and desensitization treatment, permanent and complete control of the dermatitis can be obtained; thus, the value of desensitization.

SUMMARY

The role of pathogenic and saprophytic fungi in the production of allergic dermatitis has been reviewed. Emphasis has been placed on the usefulness and limitations of skin tests in diagnosis. The desensitization treatment of atopic dermatitis due to inhalants has been discussed in detail.

REFERENCES

1. Lewis, G. M.; Sulzberger, M. B., and Wise, F.: Trichophytin and allergy to trichophytin. Arch. Dermat. & Syph., 36:548, 1937.
2. Jillson, O. F., and Huppert, M.: The immediate wheal and the 24-48 hour tuberculin type edematous reactions to trichophytin. J. Invest. Dermat., 12:179, 1949.
3. Rockwell, E. M., and Johnson, P.: The insect bite reaction; II. Evaluation of the allergic reaction. J. Invest. Dermat., 19:137, 1952.
4. Spink, W. W.: Trichinella antigen. New England J. Med., 216:5, 1937.
5. Jadassohn: Cor.-Blatt. Schweiz. Aerzte. 42:22, 1912.
6. Williams, C. M.: Dermatophytid complicating dermatophytosis of the glabrous skin. Arch. Dermat. & Syph., 13:661, 1926.
7. Peck, S. M.: Epidermophytosis of the feet and epidermatophytids of the hands. Arch. Dermat. & Syph., 22:40, 1930.
8. Traub, E. F., and Tolmach, J. A.: An erysipelas-like eruption complicating dermatophytosis. J.A.M.A., 108:2187, 1937.
9. Sulzberger, M. B.; Rostenberg, A., Jr., and Goetz, D.: Recurrent erysipelas-like manifestations of the legs: their relationship to fungous infections of the feet. J.A.M.A., 108:2189, 1937.
10. Waisman, M.: Recurrent, fixed erysipelas-like dermatophytid. Arch. Dermat. & Syph. 53:10, 1946.
11. Naide, M.: The causative relationship of dermatophytosis to thromboangiitis obliterans. Am. J. M. Sc., 202:822, 1941.
12. Thompson, K. W.: Studies of the relationship of dermatomycosis to ulceration and gangrene of the extremities. Yale J. Biol. and Med., 16:665, 1944.
13. Holmans, J. C., Jr.: Use of trichophytin in thromboangiitis obliterans. Arch. Dermat. & Syph., 55:512, 1947.
14. Year Book of Dermatology and Syphilology, ed. by F. Wise and M. B. Sulzberger, Chicago, Year Book Publishers, Inc., 1936, p. 15.
15. Wise, F., and Sulzberger, M. B.: Urticaria and hayfever due to trichophyton (epidermophyton interdigitale). J.A.M.A., 95:1504, 1930.
16. Waldbott, G. L., and Ascher, M. S.: Chronic urticaria recurring every six weeks, due to a fungous infection. Arch. Dermat. & Syph., 36:314, 1937.
17. Peck, S. M., and Schwartz, L.: A practical plan for the treatment of superficial fungous infections. Pub. Health Rep., 58:337, 1943.
18. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin. Ed. 10. St. Louis: C. V. Mosby Company, 1939, p. 150.
19. Jillson, O. F., and Hoekelman, R. A.: Further amplification of the concept of dermatophytid: I. Erythema annulare centrifugum as a dermatophytid. Arch. Dermat. & Syph., 66:738, 1952.
20. Jillson O. F.: Allergic confirmation that some cases of erythema annulare centrifugum are dermatophytids. Arch. Dermat. & Syph., 70:355, 1954.
21. Beare, J. M., and Cheeseman, E. A.: A localized outbreak of tinea capitis (M. Audouini) in northern Ireland. Arch. Dis. Child. (London), 26:149, 1951.

22. Jillson, O. F., and Buckley, W. R.: Fungous disease in man acquired from cattle and horses (due to trichophyton faviforme). New England J. Med., 246:996, 1952.
23. Kligman, A.: The pathogenesis of tinea capitis due to *M. Audouini* and *M. Canis*. J. Invest. Dermat., 18:231, 1952.
24. Naide, M.: Allergic lesions following thrombophlebitis. Arch. Int. Med., 80:388, 1947.
25. Jillson, O. F.: Unpublished data.
26. Zakon, S. J., and Taub, S. J.: The inhalation of house dust and horse dander as an etiological factor in atopic dermatitis. J. Allergy, 9:523, 1938.
27. Feinberg, S. M.: Seasonal atopic dermatitis: the role of inhalant atopens. Arch. Dermat. & Syph., 40:200, 1939.
28. Rowe, A. H.: Dermatitis of the hands due to atopic allergy to pollen. Arch. Dermat. & Syph., 53:437, 1946.
29. Tuft, L.: Importance of inhalant allergens in atopic dermatitis. J. Invest. Dermat., 12:211, 1949.
30. Tuft, L.; Tuft, H. S., and Heck, V. M.: Atopic dermatitis: I. An experimental clinical study of the role of inhalant allergens. J. Allergy, 21:181, 1950.
31. Tuft, L., and Heck, V. M.: Studies in atopic dermatitis: IV. Importance of seasonal inhalant allergens, especially ragweed. J. Allergy 23:528, 1952.
32. Jillson, O. F., and Adami, M.: Allergic dermatitis produced by inhalant molds. Arch. Dermat., 72:411, 1955.
33. Lobitz, W. C., Jr., and Dobson, R.: Physical and physiological clues for diagnosing eczema. J.A.M.A., in press.
34. Swaebly, M. A., and Christensen, C. M.: Molds in house dust, furniture stuffing, and in the air within homes. J. Allergy. 23:370, 1952.
35. Jillson, O. F., and Piper, E. L.: Inhalant allergens in dermatitis. Arch. Dermat., 71:436, 1955.
36. Marcussen, P. V.: Relationship of urticarial to the inflammatory reaction to trichophytni. Arch. Dermat. & Syph., 36:494, 1937.
37. Feinberg, S. M.: Allergy in Practice. Ed. 2. Chicago: Year Book Publishers, Inc., 1949, pp. 216-285.
38. Hansel, F. K.: Clinical Allergy, St. Louis: C. V. Mosby Company, 1953, p. 587.
39. Rappaport, B. Z.: Society proceedings. J. Allergy, 5:91, 1933.
40. Cooke, R. A.: A consideration of some allergy problems: I. Allergic dermatitis (eczema). J. Allergy, 15:203, 1944.
41. Albert, M., and Walzer, M.: Contact reactions in atopy: II. The incidence of contact reactions with various allergens. J. Invest. Dermat., 3:119, 1940.
42. Albert, M., and Walzer, M.: Contact reactions in atopy: III. Contact reactions in various atopic illnesses. J. Allergy, 14:437, 1943.
43. Sulzberger, M. B.: Discussion of contact reactions in atopy. II. The incidence of contact reactions with various allergens. J. Invest. Dermat., 3:129, 1940.
44. Vollmer, H.: Pseudoreactions to the tuberculin patch test. Am. J. Dis. Child., 78:302, 1949.
45. Kesten, B. M.: Allergic eczema. New York J. Med., 53:2441, 1954.
46. Mitchell, J. H., and Mitchell, W. F.: Seasonal dermatitis due to the albumin fraction of timothy pollen J. Allergy, 16:48, 1945.
47. Chobot, R.: Dermatitis due to pollen protein: case presentation. J. Allergy, 8:276, 1937.
48. Peck, S. M., and Salomon, G.: Eczema of infancy and childhood; contacts as etiologic agents, with particular reference to feathers. Am. J. Dis. Child., 46:1308, 1933.
49. Simon, F. A.: Cutaneous reactions of persons with atopic eczema to human dander. Arch. Dermat. & Syph., 51:402. 1945.
50. Vollmer, H., and Goldberger, E. W.: A new tuberculin patch test. Am. J. Dis. Child., 54:1019, 1937.
51. Conant, N. F.; Wagner, H. C., and Rackemann. F. M.: Fungi found in pillows, mattresses, and furniture. J. Allergy, 7:234, 1936.
52. Walker, I. C.: Causation of eczema, urticaria, and angioneurotic edema. J.A.M.A., 70:897, 1918.
53. Diamond, H. E.: Atopic dermatitis caused by inhalant allergens and its immunologic therapy. Ann. Allergy, 11:146, 1953.
54. Epstein, S.: Allergic dermatitis: present-day concepts and management. Quart. Rev. Allergy, 5:244, 1951.

CLINICAL APPRAISAL OF A NEW ANTIHISTAMINE IN ALLERGIC DISEASE

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DESPITE a veritable parade of new antihistamines and modifications of old antihistamines, no one drug answers the questions for all allergic problems. Accepting the thesis that histamine or histamine-like substances are released in the tissues in antigen-antibody reactions, it seems reasonable to attack the problem at this level. As is well known to many allergists, antihistamines have certain predictable effects, but also may have unpredictable side or toxic effects, some produced within the scope of the structure of the medications, and, not uncommonly, some effects modified by the patient's individual susceptibility. These factors vary according to the medication, and, frequently, when you obtain maximal beneficial effect you may at the same time have maximal toxic effects, which unfortunately give the patient considerable discomfort.

A new antihistamine has been used in the past six months and seems to satisfy a great deal of the criteria of efficacy and safety of antihistamines. This medication is 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate, available as Sandostene. It has been shown by Rothlin and co-workers[9] that this antihistamine has: (1) low toxicity which further is decreased when combined with the calcium salt; (2) marked histamine antagonism associated with anticholinergic and local anesthetic properties; and (3) inhibitory effect on tissue permeability manifested in various forms of experimental edema.

Our series numbered 127 patients. Of this number, fifty-eight received the syrup (orally); forty-two, tablets (orally); four, ampuls (parenterally) and twenty-three used the lotion (topically). The conditions treated were noninfective asthma intrinsic asthma, allergic rhinitis, perennial rhinitis, contact dermatitis, such as ivy and chemical dermatitis, atopic dermatitis, urticaria, drug rashes, stings from hornets or bees, and pruritus of jaundice. The above were chiefly private patients, with some from the Allergy Clinic at St. Peter's General Hospital in New Brunswick, New Jersey. The sex was equally distributed and the age varied from eight months to sixty-nine years.

Of the fifty-eight patients using the syrup*, forty-six were adults with various complaints, as shown in Table I.

The dose was adjusted for each patient. Children under thirteen received one teaspoonful every three hours; if no improvement occurred after two doses, the dosage was increased to two teaspoonfuls every three hours. Usually, one teaspoonful every three hours was adequate. The adult dose was two teaspoonfuls every three hours, which was adequate

Dr. Smith is an Associate Fellow of The College of Allergists, Inc.
*Each 4 cc contains: Sandostene 12.5 mg, Neo-Calglucon 1.353 Gm.

TABLE I. RESULTS OF THERAPY WITH SANDOSTENE + CALCIUM SYRUP

Complaint	Number of Patients	Response
Noninfective asthma	None	
Intrinsic asthma	1	Excellent
Hay fever and asthma	8	Excellent
	1	Good
Allergic rhinitis	10	Excellent
	1	Moderate
	2	Poor
Perennial rhinitis	3	Excellent
	1	Poor
Contact dermatitis	4	Excellent
	1	Moderate
Atopic dermatitis	2	Excellent
Urticaria	4	Excellent
Eczema	5	Excellent
	3	Moderate
Drug rash	7	Excellent
	1	Moderate
Pruritus associated with icterus	2	Excellent
Varicose vein pruritus	2	Excellent

for all but one patient. In this case, it was necessary to increase the dose to eight teaspoonfuls every three hours to achieve an excellent response. In ten adults, three teaspoonfuls per day seemed to achieve the same response as twelve teaspoonfuls per day. The onset of effect was within one-half hour and lasted four to six hours. There were no complaints about taste, amount or frequency of administration.

The best results were obtained in allergic rhinitis. When the rhinitis was associated with asthma, the response was almost as good, but the effect on the asthmatic state was negligible. The efficacy of the syrup was also good in allergic skin conditions. The patients' pruritus had varied etiology, such as urticaria, atopic dermatitis, obstructive jaundice, senile pruritus, chemical pruritus (e.g. Oakite Cleaner) and plant dermatitis. It is believed in these cases that the addition of calcium was most beneficial. Ninety per cent responded favorably to Sandostene + Calcium Syrup.

The syrup produced nausea in two patients, which necessitated discontinuance of the medication. Both individuals were highly emotional women, which possibly had some bearing on this problem. One child developed a sore tongue and the drug was stopped. There was no drowsiness in this group, even with eight teaspoonfuls every three hours.

The tablets were administered to forty-one patients ranging in age from six years to sixty-seven years with the various conditions shown in Table II.

TABLE II. RESULTS OF THERAPY WITH 25 MG SANDOSTENE TABLETS

Complaint	Number of Patients	Response
Allergic rhinitis	13	Excellent
	2	Moderate
Perennial rhinitis	2	Excellent
	4	Good
	3	Poor
Intrinsic asthma	None	
Urticaria	4	Excellent
	1	Moderate
Contact dermatitis	2	Excellent
Angioneurotic edema from stings	1	Excellent
	1	Good
Drug reactions (Tetanus antitoxin)	2	Questionable
Hay fever and asthma	4	Excellent
	1	Moderate
Eczema	1	Excellent

The dosage varied from one-half tablet every four hours to one tablet every three hours. In one instance it was necessary to administer two tablets every four hours to obtain a satisfactory response. In some individuals, the effect was more prolonged, thus they required only one tablet after breakfast and one tablet at bedtime. Five patients became mildly drowsy, but not sufficiently to prevent driving or continuing their everyday activity; as the medication was continued, the drowsiness disappeared. One patient experienced a mild transient vertigo. It is interesting that several patients had received other antihistamine preparations previously with no effect and did respond to Sandostene. One patient became nauseated with the syrup, but obtained a good effect with tablets, without nausea.

The ampuls* were used in five severe eczema patients ranging in age from thirty-five to fifty years. Injections were given every two days; no more than three injections were given to any one patient. After an intravenous injection of 10 cc, a flush was noted in thirty seconds, which usually subsided within ten minutes; this flush was not as intense as the flush produced by the usual calcium injection and far less than nicotinic acid. A mild drowsiness was experienced which subsided within one half to one hour. Relief of itching was almost immediate, followed with improvement of the eczema. One eczema of three years' duration, with numerous recurrent exacerbations, responded only 50 per cent. No conclusions can be obtained with five patients, but it is suggestive of the efficacy of the material.

Twenty-three patients, varying in age from one to sixty-seven years,

*Each 10 cc ampul contains per 1 cc, 5 mg Sandostene in 10% Neo-Calglucon solution.

were treated topically with the lotion. They were cases of eczema, atopic dermatitis, contact dermatitis to chemicals and plants, angioneurotic edema due to bites, and pruritus ani. Applications were as needed, usually three or four times a day. In nine patients tablets by mouth were administered at the same time. The lotion was soothing, mildly anesthetic, definitely decongestive and antipruritic, and there were no localized adverse symptoms produced by the lotion. The following patient typifies the excellent response.

A woman (housewife) aged sixty-five, with an allergic rash of the antecubital areas, with no past history of any allergy, eczema or hives, with no known chemical contacts, had not responded to three months' treatment with many different lotions, x-ray therapy, and steroids. This patient received one teaspoonful of the antihistamine + calcium syrup every three hours, with the antihistamine + calcium lotion applied topically, and revealed remarkable improvement within one week. The sedative effect of calcium was particularly impressive in this case.

All but two patients obtained excellent results. One case developed a flare-up of her eczema after one application. This, however, may have been purely coincidental. No further attempt was made to use the lotion on this patient. One other patient obtained only a fair result and required steroids for relief.

DISCUSSION

In general, beneficial effects were noted in the first few hours, as pointed out by Baker,[1] Clein,[4] Combes,[5] Dobes,[6] Parker,[8] and Saffron.[10] If none appeared, the dosage was increased; however, if no improvement was noted within twenty-four hours, medication was discontinued. No patients were continued on the therapy beyond three days if they did not respond. Dosage varied with age, but response was as good in infants as older persons. Toxic effects were minimal; if properly used, Sandostene is almost innocuous. No habituation was noted and there were no direct allergic reactions to the medication itself. The addition of calcium to both the syrup and ampuls makes the medication particularly beneficial in pruritic and allergic rhinitis cases when a maximum effect in a short period of time is required. Acute nasal and skin reactions responded particularly well to the tablets. The only side effect from the tablets was mild drowsiness in five out of twenty cases, whereas the syrup caused nausea in two out of forty-six cases. The effect on asthma was minimal to absent, except when associated with pollen rhinitis.

SUMMARY

Sandostene tablets and Sandostene + Calcium ampuls, syrup and lotion present an unusual degree of efficacy in hay fever, allergic rhinitis, perennial rhinitis, contact dermatitis, urticaria, drug rash and pruritus, with a considerably small degree of side effects. The antihistamine + calcium

syrup and the tablets were also given to children with good results without side effects.

In a total number of 127 cases (fifty-eight treated with syrup, forty-one with tablets, twenty-three with lotion and five with ampuls), one hundred and six showed good to excellent results, eleven moderate, eight poor and two questionable. Side effects (drowsiness and nausea) appeared in seven cases from the whole series.

These preparations promise to occupy a definite niche in our therapeutic armamentarium.

REFERENCES

1. Baker, K. C.: A new antihistaminic for the treatment of dermatologic disorders. Southwestern Med., 36:318 (1955).
2. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4. Baltimore: Williams & Wilkins Company, 1945.
3. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 4. Philadelphia: W. B. Saunders Company, 1950.
4. Clein, N. W.: A new antihistamine for treatment of various allergic manifestations. Ann. Allergy, 13:163 (1955).
5. Combes, F. C., and Reisch, M.: A clinical evaluation of piperidine compound alone, and combined with calcium intravenously in antihistamine therapy, J. Invest. Dermat., 24:191 (1955).
6. Dobes, W. L.: Dermatologic application of a new combined calcium-antihistamine preparation. J.M.A. Georgia, 44:81 (1955).
7. Feinberg, S.; Malkiel, S.; and Feinberg, A. R.: The Antihistamine. Chicago: Year Book Publishers, Inc., 1950.
8. Parker, W.: Further observations on the use of combined calcium antihistamine therapy in dermatology. Internat. Arch. Allergy, 7:65 (1955).
9. Rothlin, E., and Cerletti, A.: Pharmacologic studies on a new antihistamine and its combination with calcium. Ann. Allergy, 13:80 (1955).
10. Saffron, M. H.: Effective control of pruritus with a new antihistaminic-calcium combination. J. M. Soc. New Jersey, 52:357 (1955).

402 Raritan Avenue
Submitted May 7, 1956

NINTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

The Ninth International Congress on Rheumatic Diseases will be held in the Royal York Hotel, Toronto, Ontario, Canada, June 23-28, 1957. Inquiries should be addressed to: Post Office Box 237, Terminal "A," Toronto, Ontario, Canada.

NATIONAL INSTITUTES OF HEALTH

The government appropriations for the National Institutes of Health for 1957 has been increased to $216,508,000.00. Of this sum the separate institutes will be supported as follows: Cancer, $48,432,000.00; Mental Health, $35,197,000.00; Heart, $33,396,000.00; Neurological Diseases and Blindness, $18,650,000.00; Arthritis and Metabolic Diseases, $15,885,000.00; Allergy and Infectious Diseases, $13,299,000.00 and Dental Health, $6,026,000.00.

ERYTHEMA MULTIFORME FOLLOWING POLIOMYELITIS VACCINATION

Report of a Case

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POLIOMYELITIS vaccine (Salk) has now been administered to many millions of children in the United States, and to date there have been no published reports of serious reactions. The following case report, however, suggests that a sensitivity reaction may occur to some component of the vaccine.

CASE REPORT

D. K., a nine-year-old white girl in good previous health, was brought to my office for Salk vaccine and given 1 cc of the Lilly product on November 9, 1955. Two weeks later she presented on the anterior surface of both thighs a pruritic, superficial, erythematous eruption with indefinite margins, which spread to her abdomen, chest and hands. She was treated with antihistaminic agents and Nivea cream. During the following week the lesions became scaly and there were excoriations from scratching. By the second week the eruption had completely subsided.

On December 14, 1955, she was given a second injection of 0.1 cc, of poliomyelitis vaccine intradermally. There was no local reaction, but five days later the patient noted joint pains in both knees and shoulders and generalized severe pruritus. Within twenty-four hours the body was covered with an erythematous, raised eruption especially marked on the thighs, abdomen, face and arms. The eyelids were edematous. There was no elevation of temperature. Except for the skin eruption, physical examination was negative.

A trial of antihistaminic agents and starch baths for two days gave no relief. Because of the severity of the symptoms, excoriation, and serous exudation, the patient was placed on treatment with prednisone, 10 mg. every four hours, which relieved her symptoms within twenty-four hours. The prednisone dosage was then reduced to 5 mg every four hours, and forty-eight hours later to 5 mg every six hours. This dosage was continued for one week and then diminished by 2.5 mg every two days. Urinalysis, blood count and sedimentation rate were within normal limits at this time.

The history of the patient revealed that orange juice had, on several occasions, produced a pruritic, maculo-papular dermatitis of both thighs. This had carefully been avoided. There was no history of injection of foreign serum proteins. The patient had been given intramuscular injections of penicillin in 1954 and 1955 for "tonsillitis" with no untoward symptoms. The family history was negative for atopic disorders.

It is impossible to be certain that this reaction was actually due to any component of the poliomyelitis vaccine, but because of the time relationship involved it was felt that the vaccine might have been the offending

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agent. However, there is no reliable means of demonstrating this to be true. Skin tests are not absolute indications of penicillin sensitivity and the lack of any local reaction to the intradermal injection of the vaccine showed it to be of little immediate value in predicting a systemic reaction.

This case report is presented neither as an indictment of the poliomyelitis vaccine nor as a conclusion that it was the offending agent, but rather to bring this series of events to the attention of other physicians so that if other cases of a similar nature occur they may more readily be identified.

NEW APPOINTMENT FOR DR. JULES FREUND

Dr. Jules Freund, New York immunologist, has been appointed as head of the newly established research program in allergy and immunology at the National Institutes of Health, Bethesda, Maryland.

Dr. Freund was Chief of the Division of Applied Immunology of the Public Health Research Institute of the City of New York. He has made many contributions in research, one of the most important being the demonstration of the capacity of certain fatty and waxy substances to enhance the protective effect of vaccines. This has improved existing vaccines, and represents a new approach to the techniques of immunology.

A past president of the American Association of Immunologists and member of the editorial board of the *Journal of Immunology*, Dr. Freund is currently serving as chairman of the board of the Federation of American Societies for Experimental Biology. For the last several years he has also served as a consultant to the Department of the Army and to the Public Health Service.

The research program at Bethesda which Dr. Freund will direct is being established as one of the major divisions of the National Institute of Allergy and Infectious Diseases. Studies will be directed toward such areas as investigation of the nature of antigens, the formation of antibodies, and the reactions between them; exploration of the basis for hypersensitivity of tissues and its importance in disease; and extension of knowledge concerning the role of cellular immunity in the outcome of disease.

Dr. Freund was born in Budapest, Hungary, and received his M.D. degree and Certificate of Public Health from the Royal University Medical School, Budapest. After service as a medical officer in the Austrian Army in World War I, he returned to Budapest to serve on the faculty of the University Medical School, and came to the United States in 1923.

Progress in Allergy

DERMATOLOGIC ALLERGY

Critique and Review of the Recent Literature

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INTEREST in dermatologic aspects of allergy continues to fill the American and European literature. Fuel to the fire is added by the multitude of new drugs and reactions resulting from their widespread use. The steroids have revived the interest of the experimentalist, the specialist and the general practitioner in affairs allergic. The current controversy on atopic dermatitis is a healthy outburst of ideas dermatologic, allergic and psychosomatic. The establishment of a national organization for the study of allergic disease should prove stimulating. At least two medical schools now have professors of dermatology who are interested in the experimental approach to the problem of dermatologic allergy. For all these reasons, progress should be expected over the coming months and years, which it is hoped will help us better to understand the pathogenesis of allergic skin diseases.

For the convenience of the reader this review is divided into the following subsections: (1) allergic eczematous contact dermatitis; (2) atopic dermatitis; (3) urticaria and angioedema; (4) drug eruptions; (5) steroid hormones, and (6) miscellaneous allergies.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Experimental Studies.—In patients with eczematous allergy it is possible to produce local eczematous reactions by electrophoresis of the antigen into the skin. Resulting reactions are quite similar to those that can be elicited with ordinary patch tests. The method is particularly suitable in dealing with metallic salts and offers the advantage that the skin area involved is uncovered so that the reaction can be followed throughout its course. Moderate freezing with carbon dioxide snow or ethyl chloride weakens or abolishes the eczematous reaction. Haxthausen[101] found that slight freezing, slight burning and ultraviolet radiation have a distinct inhibitory effect on eczematous reactions. X-rays (Bucky) and continuous beta radiation (P_{32}) have not inhibited the reaction. On intracutaneous injection, arsenic produces inhibition of the reaction even when it is employed in concentrations so low that it affects the normal skin but slightly. Several substances playing a role in enzymatic processes were found to have no effect on the eczematous reaction. Among substances employed therapeutically, antihistaminic ointments were found to have no effect on the eczematous reaction, whereas hydrocortisone in the form of ointment showed a slight inhibitory effect in a few instances. Hydrocortisone injected intradermally was a potent agent in blocking the eczematous reaction.

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Seven hundred and forty-three patients were studied by Baer and others[17] to determine the incidence of existing allergic eczematous contact type hypersensitivity to a series of topical therapeutic agents. Each patient received from one to forty tests and only agents that had been tested in fifty or more patients were recorded. Such substances as benzoic acid, benzyl benzoate and ichthammol showed no positive reactors. The index of sensitivity was below 2 per cent for boric acid, aluminum acetate, menthol, naphthalan, petrolatum and phenol; it was between 2 and 5 per cent for aquaphor, hydrous wool fat, resorcinol, salicylic acid and vioform. An index of sensitivity above 5 per cent was seen for the mercurials, benzocaine, crude coal tar and compound benzoic and salicylic acid ointment. It is important to rule out primary irritants and to remember that a patch test negative on normal skin may be irritative for the diseased skin.

Many studies implicate the regional lymph node and its functions in sensitization experiments. Rostenberg and Best[215] made cytologic studies of the regional lymph nodes at various stages in the development of sensitization. They found no changes which suggested that the regional lymph node plays any special role in eczematous sensitization. These authors believed that the cutaneous reticuloendothelial system is capable of performing the role of a regional lymph node. It is suggested that the complete antigen is made in the epidermis or upper cutis in simple chemical sensitizations. The appropriate local cells in the dermis (possibly primitive reticulum cells) develop an enzymatic adaptation which the authors thought is the basis for sensitization. Cells so sensitized would transfer this adaptation to daughter cells to maintain the sensitivity. There is evidence that antibodies can be manufactured locally in the skin. Attempts to investigate the fundamental basis for itching have yielded a new approach. Shelley and Arthur[14,229] presented evidence for an enzymatic basis for itching in man. It was demonstrated that the active pruritogenic principle of cowhage (Mucuna) is a proteinase called mucunain. They used a wide variety of enzymes and only proteinases were active as chemical excitants of itching. They introduced intraepidermally one or more of the tiny spicules which cover the cowhage pods. Of sixty subjects studied, all experienced itching after the material was rubbed on the forearm. There were no previous contacts with this preparation in any of the subjects. The itching appeared within thirty seconds and continued for about three minutes. Itching could be produced by the careful introduction of one of these spicules without stimulating erythema or whealing. Removal of the epidermis by scotch tape stripping left a site which could not be stimulated by cowhage. Autoclaving the material at 250° C for thirty minutes rendered it inactive. Control attempts at producing itching with other spinous and irritant fibers such as cactus spines and glass wool were unsuccessful. Simple distilled water extracts of cowhage were easily made. It was found that the extract was unstable at room temperatures but could be kept in a frozen state for over three months. Inactivation followed changes in hydrogen ion concentration, heating or any simple denaturant process. The active principle appeared to be an endopeptidase and was called mucunain. Although most studies on pruritus have been on a neurophysiologic basis, these investigations introduce a pure biochemical approach which is new. Interesting comments on contributions to dermatologic allergy may always be read with profit in the *Year Book of Dermatology and Syphilology*.[269]

Gaul[86] was interested in comparing the effect of contact tests in chromate sensitivity using moistened filter paper squares with several dilutions of aqueous potassium chromate. This was compared with a technique of splashing or wetting of the skin with similar preparations to imitate a clinical exposure. A dermatitis could be exacerbated after healing by wetting the skin with a dilution of 0.1 per cent of aqueous potassium chromate. Chronicity may be maintained by dilutions of as little as 0.01 per cent and probably higher. Morris, who has been interested in this problem, has a patient with exquisite chrome sensitivity who will react to 0.00001 per cent chromate solution.* It is to be noted that testing for metal sensitivity in the presence of an extensive dermatitis may produce positive reactions of no diagnostic significance. On the other hand, the persistence of a positive reaction for several weeks is strongly suspicious of etiologic hypersensitivity. Unless extreme hypersensitivity is suspected clinically, a concentration of aqueous potassium chromate from 0.1 to 1 per cent may be used for patch tests. Nørgaard[165] applied 10 microliters of different strength solutions of nickel sulfate tagged with radioactive Ni_{57}. These solutions were applied to the skin and after evaporation were covered with foil and adhesive. The radioactivity which remained was measured immediately and again in twenty-four hours. Nørgaard found that two-thirds of the nickel is resorbed (decrease of radioactivity) in twenty-four hours both in normal persons and persons hypersensitive to nickel. By the time the eczematous dermatitis appears in hypersensitive individuals, only about 10 to 15 per cent of the resorbed quantity of nickel remains in the skin. Reduction of radioactivity by two-thirds in twenty-four hours may be due to penetration deeply into the skin or to the circulatory effect of lymph vessels and capillaries. It is estimated that the tagged nickel must penetrate about 2 mm into the skin if radiation is to be completely absorbed. It is to be remembered that when the antigen has penetrated about 0.1 mm of tissue it has already reached the corium with its lymph and blood vessels. Everall et al[68] demonstrated that nickel containing an antigen complex was more active clinically than the simple salt. Patients vary in their reaction to nickel chloride and some patients react to higher concentrations than those found on normal exposure. Of twenty-eight patients sensitive to nickel by previous positive patch tests all were still sensitive when retested.

Inactivation of industrial allergens was studied by Rajka and others[197] who showed that the application of a 1 per cent vitamin C ointment to the skin eight hours prior to a patch test in chrominum-sensitized persons may inhibit the usual allergic reaction. A stabilized vitamin C ointment was made by the addition of a 1 per cent calcium sodium-ethylene diamine-tetra-acetic acid preparation to the mixture. In animals the caustic effect of a 20 per cent solution of potassium bichromate could be prevented by the addition of 5 to 10 per cent vitamin C. These studies are further attempts along the line of the chelating agents which modify allergic sensitization reactions by some means other than the immunologic mechanism. Thurmon and others[249] reported various chemical, biologic and clinical tests with poison ivy and its absorption by amberlite ion exchange resins. The amberlite exchange resins used in this experimental work were found to remove effectively urushiol from solutions. The preparations were then compared in protection and prevention patch test experi-

*Personal communication.

ments with substances such as Kerodex, Covicone, zirconium oxide, hydrocortisone and Prantal cream. In the order of clinical effectiveness, the resins XE-87-2 and XE-87-3, the zirconium oxide cream and Prantal cream (Schering) were the most efficient as barrier creams.

Viable white blood cells were obtained from the blood of five persons suffering from eczematous contact type sensitivity. These cells were injected intraperitoneally into five guinea pigs. After twenty-four hours, skin tests by inunction were made on the epilated flank of each recipient animal using a small drop of the antigen to which the human subject had a known sensitivity. The agents used include resorcin, paraphenylenediamine, nickel sulfate and turpentine. Patch tests were then read after twenty-four to forty-eight hours and similar tests using inunction of the antigen were used on other sites and repeated on the second day after injection of the cells and also on subsequent days. Rosenthal and others[212] concluded that since a positive patch test reaction did not occur on any of these tested sites, the allergic eczematous contact type sensitivity was not transferable by this procedure. Passive transfer of allergic eczematous hypersensitivity in man has not been regularly and successfully accomplished using injections of serum or of white cell concentrates from sensitive donors. Dogliotti[57] used a solution of gamma globulin, 0.1 cc, from a sensitized person who had been previously exposed to dinitrochlorbenzol. In 62.5 per cent of subjects a positive reaction was noted, characterized by erythema lasting for twenty-four hours followed by edema and vesiculation. Although much laboratory work has been done on the experimental animal, it is not possible to produce regularly eczematous changes in the skin of the commonly used laboratory animals. Exceptions to this are the guinea pig nipple and the foot pads of rats and guinea pigs. Jadassohn et al[113] found that eczematous changes could be produced in guinea pigs sensitized to dinitrochlorobenzene. If colchicine was given, a strong reparative posteczematous mitotic flare-up was seen at thirty-three and 129 hours. Further studies using the guinea pig nipple indicated that there was no parallelism between the epidermal alterations and the inflammatory dermic alterations. This is true in human eczema as well. A continuation of previous studies on sensitization of the human skin was reported by Grolnick.[96] He reviewed the present data for prophetic testing to meet the requirements of the U.S. Food and Drug Administration on new products. Present methods acceptable to the administration and recommended by Draize are cumbersome. It had been shown that 87 to 90 per cent of patients could be rendered sensitive by one or two-day tests made at weekly intervals until sensitization occurred. Seventy-two per cent of patients could be sensitized by single seven day patch tests. Using a new preparation 2-nitro-2 bromo-1 methoxy-1-phenylpropane, Grolnick planned patch tests close to each other and at great distances from each other. Exposure time was also varied, tests being applied for one, two, three, four and seven-day periods with the total testing time ranging from thirty-one to thirty-eight days. Controlled testing with a 1 per cent concentration of this preparation in a water soluble ointment ruled out the possibility of a primary irritant with this agent. The subjects used were volunteer college students. Of the various methods used 32 per cent sensitization was obtained with the method resembling the seven-day patch test and to the distribution of the patch test sites over a small area of skin. Contact dermatitis of the palms and soles is much less frequent than of other adjacent areas and

this may be due to the thickness of the stratum corneum. Spier and Sixt[237] stated that contact dermatitis results when sensitization of living epithelial cells occurs with direct contact between sensitized cells and allergen. The stratum corneum may interfere with the latter. To test this finding the authors arranged for quanitative stripping of the skin with adhesive tape to remove cell layers before doing quantitative patch testing on these stripped areas. After six strippings it was found that the allergen concentration required for a response was reduced by about 10 per cent. Decreasing the stratum corneum by 50 per cent, sensitivity of the area was increased about thirty times. These factors hold for water soluble antigens. It was found, however, that for mercury compounds the reactions did not depend on concentration or thickness of the stratum corneum, or both. Three commercial synthetic detergents were used in a study by Pätiälä[171] and others to test the irritation of the skin by these agents. One preparation was a secondary alkyl sulfate, the second an alkyl benzene sulfonate and the third a polyethylene-oxide condensation product. Various concentrations of detergent from 20 to 0.2 per cent were applied to the backs of fifty-two dermatologic patients; 249 normal subjects were used as controls. Negative patch tests were obtained in 48 per cent of the dermatologic patients; 32.5 per cent of the normal controls had positive reactions. In both groups, however, there were no reactions in the 0.2 per cent strength patch test. Commercial concentrations recommended for use are lower than 0.2 per cent and it seems unlikely from this evidence that skin irritation will develop from the use of detergents according to the manufacturers' instructions. Here again it must be remembered that patch tests do not always reproduce the clinical conditions under which an agent is used. The normal lipid layer of the skin was not affected by washing with water or alcohol according to Ramsay and Jones.[199] Washing with soap and water, however, significantly lowered the skin fat factor. By dissolving soap in water and acidifying with dilute sulfuric acid a water emulsion of fatty acids was obtained. It appeared that a layer of soap can be adsorbed on the skin to give a layer of free fatty acids on the skin. Certain fatty acids could produce allergic reactions but others may be bacteriostatic or bactericidal and therefore beneficial.

Albino guinea pigs were sensitized with 2,4 dinitrochlorobenzene and, by challenging with six concentrations of the drug, it was possible to titrate the approximate degree of sensitivity of the animals, according to Rockwell.[207] Factors affecting this sensitivity could then be determined. Irritation by various methods had variable effects on sensitization. Sandpapering the skin before application of the allergen increased the degree of sensitization. Repeated applications of nonirritating concentration of croton oil on the same area resulted in chronic irritation. Severe inflammation with croton oil, however, decreased the degree of sensitization to 2,4 dinitrochlorobenzene. Fowler's solution given to the animals decreased the degree of sensitivity. It is thought that most substances which are allergens produce both contact and anaphylactic reactions. An attempt was made by Mayer[154] to clarify the relationship between contact (delayed) and immediate type of specific sensitizations in skin allergies. It is generally believed that anaphylactic sensitization depends primarily on the mechanism of the host and that the chemical nature of the allergen is secondary. In contact sensitization the nature of the allergen is of prime importance and the role of the host of secondary interest. Contact

with paraphenylenediamine produces primarily a contact dermatitis but inhalation of the volatile oxidation products or the dry powder has been known to produce asthma. It has been suggested that contact dermatitis becomes established when a hapten combines with proteins derived from the skin. Perhaps asthma appears if the hapten combines with proteins of the lungs. Mayer had shown previously that the application of paraphenylenediamine to the skin of guinea pigs produced contact dermatitis and the subcutaneous or intraperitoneal injection of the same allergen produced anaphylactic sensitization. A study of 111 patients with paraphenylenediamine allergy revealed that fifty had dermatitis, forty-three asthma and eighteen a combination of asthma and allergic skin lesions. Six of the latter group had generalized neurodermatitis and twelve had contact dermatitis. Patch tests on all eighteen were positive to paraphenylenediamine. In some patients the evolution from contact dermatitis to neurodermatitis was so gradual as to be confusing. This may be due to a change of exposure to the allergen.

Investigations into the role of the peripheral neurovegetative system and its relationship to sensitization studies were made by Ramos e Silva.[198] Sensitization to dinitrochlorobenzene was studied in six patients who had areas of cutaneous anesthesia due to nerve damage from leprosy. Ten per cent dinitrochlorobenzene was applied to a small skin area and after fifteen days a patch test was made with the same antigen, using 1:500 and 1:1000 dilution. Patch test results after fifteen days were positive on normal skin or within the anesthetic areas. If the original application was made to the anesthetic skin, it required a higher concentration of the antigen to produce positive patch tests on either area. These results suggest that there is no considerable participation of the neurovegetative system in the mechanism of sensitization. Polák[179] begins with the assumption that skin sensitization may be a reflex action. Using animals, he found that afferent nerve fibers of the abdominal sympathetic and of the somatic nerves could be cut and areas of prospective sensitization be entirely denervated. Once the animal is sensitized, the cutaneous response to test doses is equally positive above and below the severed afferent nerve fibers. The author found that sensitization in newborn and grown guinea pigs does not differ, although it is known that the central nervous system of the newborn is said to be incompletely developed. Sleep produced by drugs inhibits sensitization. From his findings, the author believed that sensitization is caused by reflex action. The antigen applied to the skin stimulates the receptors of the skin and the stimulus is transmitted by way of the afferent fibers to the central nervous system. This stimulation is then transmitted through efferent fibers to organs connected with lymphopoiesis. It is then assumed that because of this system an altered lymphocyte is formed which passes into the circulation. Contact of the antigen with these lymphocytes then produces allergic reactions.

Clinical Studies.—Alden[1] distinguishes between "industrial accident," by which is meant an event which takes place fortuitously and suddenly at a fixed time and without one's foresight or expectation, and "occupational disease" which is usually construed as one which results from the nature of employment. An industrial dermatitis is any inflammatory disease of the skin in which occupational exposure can be shown to be a major causal, contributory or eliciting factor. The proof of an industrial dermatitis depends upon medical considerations. The criteria of the first

order are: (1) inception of the eruption (when? where? how?); (2) amelioration of the eruption by cessation of work, and (3) recurrence of the eruption on return to work. The criteria of the second order are: (1) Eruption occurs first in, and is confined to, maximal areas of exposure. (2) Character and localization conform to the character and localization of an eruption of nonindustrial hazard. (3) Application of causal agents by properly applied patch tests produces a similar reaction to that of the dermatitis. (4) Other workers are similarly affected. (5) Eruption appears soon after work begins on a new potential hazard. (6) Eruption can be shown to be of the type which may result from sustained industrial exposure. It must be shown that an eruption is not of a nonindustrial nature, such as psoriasis or lichen planus. The large majority of cases of occupational dermatitis are due to primary irritants and only a small percentage are due to sensitizing agents or allergy. The entire aspect of rehabilitation of patients who suffer from industrial dermatoses was reviewed by Noojin.[166] This included a discussion of the physician who manages these patients, the employer, the insurance carrier, the role of the labor union and governmental agencies. The problem was often complicated by the patient, the doctor, the insurance carrier or the employer. Switching a patient from one job to another often means loss of seniority rights and results in financial loss to the patient. Most patients with industrial dermatoses are not very ill and yet their prolonged disability may lead to intense boredom. The slow recovery and economic loss may further delay their improvement. The solution is a difficult one requiring intensive study and social, legal and legislative reform in some instances.

Dermatoses caused by exposure to cutting oils are common eruptions among industrial workers in America.[51] These eruptions are seen in lathe and drill press operators, tool makers and others who are constantly exposed to these oils used in various industrial operations. They comprise 10 to 15 per cent of all eruptions seen by dermatologists. There are over one half million employed machinists and tool makers in the United States and a survey of the membership of the American Academy of General Practice notes that 94 per cent of its members "see industrial cases." Cutting oils are of several types: insoluble oils (true cutting oils), soluble-type products, chemical coolants (alkaline coolants), and sulfurized fats and kerosene. The insoluble cutting oils are usually insoluble oils of the paraffinic or napthenic types. They comprise straight mineral oil or oil to which elemental sulfur has been added. Sulfurized fatty oil containing 6 to 8 per cent sulfur is used for heavy cutting operations. Additives containing sulfur or chlorine or both may be added to the above oils. Soluble type products are usually mineral oil and emulsifiers such as petroleum sulfonates and soaps. Bacteriostatic agents, such as phenols and cresols, may be added. Chemical coolants are frequently made of sodium nitrite plus an amine such as triethanolamine plus water and a dye, usually fluorescein. For honing operations sulfurized fats and kerosene are used. Cutting oils are used primarily to allow high production, fast cutting and a good finished surface to the machine part. They lessen friction, cool and lubricate parts and preserve the cutting tool tips. The following eruptions have been caused by cutting oils: comedones, folliculitis, erythema and defatting of the skin, eczematization, granulomas, melanoderma, infected wounds and chloracne. Conventional patch tests admittedly do not always reproduce actual work conditions, thus they can easily be interpreted falsely. When specific hypersensitivity to

one of the ingredients of cutting oils or solvents does develop, however, properly applied patch tests are usually positive.

Beryllium is used in the fluorescent lamp industry in the form of beryllium-copper alloys in the manufacture of electrical equipment and special springs. It may cause both visceral and skin diseases. Many cases of pneumonitis in beryllium workers and of beryllium granuloma of the skin have been reported in this country. Sneddon[236] reported the case of a twenty-five-year-old woman in whom pulmonary and skin changes of sarcoid-like granulomas developed following exposure to beryllium. This patient was a trimmer of beryllium-copper alloy strip for three and one-half years. She was found to have a pulmonary granulomatosis similar to delayed chemical pneumonitis due to beryllium. She also had an eczematous hypersensitivity to beryllium shown by positive forty-eight hour patch test to high dilutions of beryllium salts and a further delayed sarcoid reaction in the skin used for the patch test. It has been known that beryllium ions attach themselves rapidly to protein and it is likely that a beryllium protein compound acts as a sensitizing allergen for the skin. A delayed sarcoid reaction appeared when the beryllium was applied to the skin. If the dermis responds to the presence of beryllium in this way, it is possible that the lung responds in the same way and the delayed chemical pneumonitis can thus be explained as an acquired hypersensitivity.

Dermatitis from adhesive tape is seen frequently.[217] This may be due to the trauma of removal or irritation by the adhesive combined with retention of sweat and serous discharges of the skin with maceration of the horny layer. In addition, there may be a disturbance of the bacterial flora by selective antibacterial action of some constituent of the adhesive and eczematous sensitization to some agent in the adhesive or in the rubber. Eczematous reactions are most frequently due to a resin colophony, crepe rubber proteins, antiseptics or complexes in the plaster mass. Reactions to the plasticizer or to the antioxidants added to the rubber have not been observed. Although mild and temporary irritant reactions due to adhesive tape are commonly seen, especially in patients with an active dermatitis, the incidence of true allergic contact sensitization dermatitis to adhesive tape is relatively low. A four-year-old girl developed large bullous lesions of both feet after wearing a new pair of patent leather shoes.[183] Dermatitis produced by allergic hypersensitivity to shoe materials appears as a rule on the dorsa of the toes and feet and especially the dorsum of the great toe, on the pressure areas on the sole of the foot rather than between the toes, as is most common in fungus infections. As reviewed in *Progress in Dermatologic Allergy, 1955,* Shatin and Reisch (Shatin, H., and Reisch, M.: Dermatitis of feet due to shoes. Arch. Dermat., 69:651, 1954) reported that a number of steps may be taken to determine this type of sensitivity. Hollander[108] described a fifty-four-year-old woman who had a persistent, pruriginous, disseminated, erythematous, squamous dermatitis of two years' duration on the neck, face, scalp and upper part of the body. Elimination of a hand lotion, a shampoo and a face cream resulted in some improvement. After a sharp recurrence, it was noted that the patient was wearing a scarf made of silk fabric into the meshes of which metallic silver strands were woven. This was found to be the primary cause of her dermatitis. In answer to a query regarding magnesium as a cause of dermatitis it was stated that in magnesium founding, ammonium borofluoride or other fluorides commonly introduced into the

mold must be considered.[188] If machining operations constituted the work, cutting oils may be the cause. Sometimes nickel dermatitis occurs in magnesium workers because of the combination of this metal in certain magnesium products. Subcutaneous tumors from magnesium slivers also occur. Metallic magnesium by itself does not seem to cause allergy or dermatitis.

Eisenberg[65] reported three cases in which contact dermatitis developed on the ear lobes and in the external auditory canals associated with the use of selenium sulfide shampoo. It had been present for at least two months in each patient. Patch tests were positive for diluted selenium sulfide. It is important to remember that dermatitis resulting from sensitivity to a shampoo may appear on the neck and the ear areas rather than on the scalp. In some patients, noted by the reviewer, excessive oiliness of the scalp will develop following indiscriminate use of selenium sulfide shampoo. Sheard[228] studied a woman, aged thirty-five, who had a contact dermatitis of the left and right fourth finger and adjacent areas. For a number of years she had worn two platinum rings without any difficulty. Detergents, caustics, and household cleaners were ruled out by careful investigation. Reactions to patch tests with platinum and iridium were positive. For many years sensitivity to platinum, gold and silver was exceedingly rare but this investigation would indicate that in some patients the index of suspicion should extend to these fine metals. The extensive use of cured epoxy resins is new in American industry. These resins are used for potting (encapsulating) electrical components to protect them from weathering and for laminating or bonding layers of flat material such as fiberglas. In addition, they are employed for casting and adhesion, and are used extensively in the aircraft industry and elsewhere. The frequency of sensitization to these agents will increase as the resins appear in various industrial fields. Patch testing has been performed using 20 per cent epoxy resin in castor oil, 20 per cent catalyst in castor oil and finally the solid resulting from reaction between the two. Rules for the prevention of this eruption in industrial plants are outlined.[224] Not infrequently cases of dermatitis due to the ingredients of ink eradicator are seen.[187] The active agents in the respective solutions are tin chloride and sodium bisulfite. Both these substances are credited with the capacity to produce mild dermatitis. The proper method of testing for these agents has previously been recorded in the *Journal of the American Medical Association,* October 2, 1954, p. 497. Rodman[208] discussed the potentially harmful household products which may act as contactants or be ingested by patients, especially children. Five excellent tables accompany this article which give the individual ingredients of many common household products including polishes and waxes, paint solvents, cleaning and bleaching agents, cosmetics and miscellaneous household preparations. These tables are useful because many manufacturers are secretive about details of the contents of the commonly used household products. The tables contain specific data helpful in the investigation of contact sensitization to household agents. A formidable list of agents in which formaldehyde may appear is presented by Baer.[16] Formalin exposure may appear in individuals who are gluers of labels, book binders, lithographers, glue barrel washers, laboratory cleaning women, pathologists and hair dressers. Painters, plywood workers and bakelite workers contact formaldehyde resins; the agent may also occur in insecticides and in general medicine.

Chrome dermatitis is reviewed in an editorial in the *Lancet*.[3] There are fifty or more occupations involved in the use of chromates ranging from electroplating to glass frosting, rubber mixing and paper hanging. The role of chromate and cement dermatitis has only lately been brought to light. A new source of chrome dermatitis is cooling fluid of diesel engines in which chromates are included to inhibit rusting. Samitz (Compens. Med., 6:7, 1954) was impressed by the chronicity of his cases of chrome dermatitis which he thought might be due to the persistence of the allergen in the skin in the form of chromium protein complexes. Morris[159] has described cases of chrome dermatitis from a glue made out of scrap chrome leather. In France a great deal of housewives' dermatitis of the hands is due to chromates in proprietary solutions of hypochlorites. It is known, however, that bleaches without chrome are equally satisfactory. The problem of chromate sensitivity was also studied by Samitz.[221] Two common exposures which cause some difficulty today appear among cement workers and railroad employes working with diesel locomotives who come in contact with chromium compounds. It is of interest that workers in the mining industry working with chromate ores show no effects on skin and nasal mucosa, but such disorders are common in the chromate producing industry and in the production of consumer goods. It is known clinically that chromate dermatitis will persist for months after the removal of the patient from the source of exposure. Patients with lesions of the skin and mucous membranes should be treated promptly to minimize the danger of chronic systemic absorption of these compounds. A number of patients sensitive to chrome glue were studied by Morris.[159] Chrome glue is manufactured from chrome-tanned leather scrap. Two patients are described who had a persistent eruption due to chrome glue which flared from wearing chrome-tanned leather shoes. It is of interest that two patients sensitive to chrome can wear chrome leather shoes if plastic freezing bags are placed between stockings and shoes.

The causes of hand eczema may be multiple and varied. It is quite likely that most of these eruptions of the hands are attributable not to a single factor but to several primary or predisposing factors. For this reason a classification kept in mind is extremely helpful. According to Bluefarb,[24] the five most common dermatoses on the hands are: (1) contact dermatitis, (2) eczematoid ringworm, (3) sweat retention syndrome (dyshidrosis), (4) atopic dermatitis and (5) nummular eczema. Contact dermatitis is usually on the dorsum, often bilateral, showing redness and bullae, and usually superficial. Diffuse, poorly defined patches are present with intense inflammatory reaction and itching. Removal of the source and investigation with patch tests led to a favorable conclusion of the case. In eczematoid ringworm, the eruption is bilateral and usually on the palms. Sharply defined deep vesicles or bullae may be seen. Inflammatory reaction is variable and itching is moderate to severe. It occurs more often in the summertime, with almost spontaneous clearing at times but a tendency to recur. A culture proves the cause. Nummular eczema occurs on the dorsum as unilateral or asymmetrical papules, vesicles or pustules which are superficial. Patch formation is the rule with sharp definition, moderate inflammatory reaction with little to moderate itching. It occurs more often in the wintertime and recurrences are common. It may be precipitated by use of soap and alkalis and may be more frequently found with the advent of modern detergents. Manage-

ment of these patients is tedious, painstaking and, at best, palliative. Cotton lined rubber gloves should be used routinely for protection of the hands. Boric acid solution may be used for hand cleansing. Silicone protection ointments have been disappointing. Topical application of 1 per cent hydrocortisone ointment or 0.1 per cent Florinef ointment used during the day with 2 per cent ichthyol ointment at night is an excellent combination. Atopic eczema occurs on the dorsal surface of the hands and it is usually bilateral and symmetrical. Vesicles are rarely seen clinically. The eruption is superficial to form diffuse patches which are poorly defined. Itching and inflammation may be intense and the eruption is more common in the wintertime. The management of atopic dermatitis of the hands is no different from the management of this disorder when it is located in the usual areas. The sweat retention syndrome or dyshidrosis occurs on the palms, usually bilaterally and symmetrically. The primary lesion is a deep vesicle, often grouped with sharp definition and very slight inflammatory reaction. Intense itching and burning occur at the onset and later mild itching appears. As a rule, the eruption occurs in the spring and summer with spontaneous involution and frequent recurrences. Fifty-seven patients with hand eczema were given patch tests by Jambor and Suskind[115] to common contact agents including different soaps and detergents. No specific reactions with commercial soaps and synthetic detergents were found by patch test nor confirmed by usage tests. The cause for the dermatitis was found in about 30 per cent of the cases and included chromate, nickel, lathe coolants, dyes, petrolatum fractions and lanolin. Further experiments were done with twenty-two patients, in which the right hand of these patients was immersed in about 0.5 per cent solution of soap or detergent at 105° F. for thirty minutes. The control hand was immersed in tap water the same temperature. Various examinations were made including pH determinations of the cutaneous surface and studies on the degree of erythema. No lasting irritation was found in this experiment. It is more than probable that mechanical irritation and other factors play a role in the pathogenesis of hand eczema. A sudden rise in pH was found to be simultaneous with the appearance of a fresh exudative exacerbation. Patients who had normal or excessive sweat secretion were able to neutralize alkali more rapidly than those with hyperkeratotic or scaling skin.

Jillson and Piper[119] established certain criteria for the diagnosis of dermatitis of the hands and other regional eczemas to stress the influence of inhalant allergens in dermatitis. These criteria consist of a positive twenty-four to forty-eight hour papular type of response (or a delayed one week eczematoid response) to the intradermal skin test using the suspected antigen; a flare-up of the dermatitis coincident with or shortly after reaction to the cutaneous test becomes positive; seasonal incidence agreeing with the positive skin reaction, and control of the dermatitis after removal of the causative allergens or proper desensitization. The routine strength of allergens is used for testing purposes. Test substances usually are pollens, inhalants, fungi and staphylococcus ambotoxoid, 1:20 dilution. Desensitization is accomplished by subcutaneous injections of 0.1 cc of the strength of extract that fails to produce a systemic flare-up or large local reaction. Doses are kept small. Desensitization was continued for a year or longer. In fourteen cases that fulfilled the strict criteria, results were excellent. In others the results varied. This is in the nature of a

preliminary study to stimulate others in this particular approach. The reviewer believes this article to be a significant contribution which allergists should study carefully and apply the principles to the management of their own cases. Bettley[22] suggested that the main differences between industrial dermatitis and housewives' hand dermatitis arise from the peculiar social, psychologic and financial significance of dermatitis which is contracted in the course of paid employment. A number of cases are cited in which it is obviously of advantage to the employe to maintain a compensable industrial dermatitis. In England the law at present provides that if the onset of the eruption is accepted as being industrial, then all of the consequences must be accepted also.

The historic and biographic background of poison ivy was carefully reviewed by Rostenberg.[214] This is an interesting, informative paper that includes observations by Capt. John Smith (1579-1631), botanists and naturalists who made contributions to the subject. The work is brought to fairly recent times with the observations of Sulzberger and Katz who found that application of the contents of poison ivy blisters by the patch test technique did not produce new lesions on sensitized individuals. The active dermatitis-producing principles of poison ivy are a group of closely-related catechol derivatives with long unsaturated side chains, the most active probably being N-pentadecylcatechol. This agent when placed on the skin unites with the body protein, presumably in the epidermis. The new conjugated protein is treated by the body as an antigen and it is Rostenberg's idea that in certain cells an enzymatic adaptation occurs toward it which continues in the daughters of these changed cells. An inflammatory reaction then follows when these altered cells again meet the antigen. Dermatitis venenata from tree pollen oils was described by Lovell and others.[136] It is well known that trees (particularly the conifers whose sap is used for preparing pitch and turpentine) have contributed to the contact dermatitis problem. Carpenters, painters and wood cutters have also been shown to be hypersensitive to turpentine and sawdust. A dermatitis occurring on the exposed area during April and May was described in three patients, who had typical lesions of plant dermatitis on the exposed areas of the skin. Two patients tested gave positive patch reactions with the ether soluble fraction of tree pollens. Oral hyposensitization with pollen oil caused an excerbation out of season in the dermatitis of both patients, and therefore one patient discontinued treatment. Although dermatitis from tree pollen oil is a rare entity, it should be suspected in patients who show a seasonal dermatitis during the tree-pollinating seasons.

A number of commonly used skin protective ointments were tested by Shaw and Crowe[227] to compare their protective efficiency against soap and water washings, soluble cutting oil washings and heavy cutting oils. The preparations entering into this study included a vanishing cream Covicone, Kerodex, various strengths of silicones in petrolatum and bentonite and other commercial protecting agents. Many of these preparations have been and are being extensively used in industry to prevent industrial dermatoses. A mark was made on the skin with water-soluble ink and then the protective ointment was rubbed over the area. The degree of protective efficiency was determined by the time required to remove the ink. A phenolphthalein indicator was also used in a similar fashion measuring the efficiency with the application of dilute potassium hydroxide on the indicator. A preparation containing 30 per cent silicones

in petrolatum gave the greatest protection. Preparations in a vanishing cream base were not highly effective. The nonsilicone preparations were of little value. For protection against either soap or oil, repeated applications of the silicone preparation in petrolatum were necessary. Various protective creams were also studied by Carrie[37] using the positive patch test technique. Patients with a known positive patch test were used. The cream was applied to the normal skin and then the excess removed after ten minutes and the test substance applied to the area. Controls were used on the opposite arm. The protective creams prevented irritant effects from such preparations as 15 per cent phenol, 25 per cent formalin and 50 per cent chromic acid in about 30 per cent of test patients. Here again it was found that an ointment base, such as lanette ointment, was particularly useful. Using alkaline test substances such as sodium hydroxide and ammonium thioglycolate the irritant effects were prevented in about 40 per cent of test patients. When comparing the effectiveness of various preventive or protective creams, however, it was found that they were not superior to commonly used ointment bases such as Eucerine or lanette wax ointment. Järnecke[116] reported his experience with a silicon protective ointment consisting of methyl polysilicon oil in a nonirritating wax base. This preparation combined with wax forms a film which spreads a protective layer on the skin which excludes dirt, water and watery solutions. Patch tests were made with a pure silicon oil on fifty-two persons and showed a low index of sensitivity. One hundred and forty-eight workers with industrial dermatoses treated with the silicon protective ointment showed gradual improvement of the eczematous lesions. Failures were observed in five of the 148 patients. The reviewer notes that most of the silicon preparations available in this country have failed to produce striking protection in many industrial situations. It is also thought that their use should be restricted to prevention rather than treatment.

Simons[234] modified the well known Unna's boot by using a plaster cast type of bandage for 100 eczematous patients treated at home. A total of 103 patients suffering from some type of eczema with itching were included in the investigation. These cases included flexural eczema, atopic eczema, and chronic allergic eczema. Cure or great improvement was obtained in over 50 per cent of the patients in two weeks' time. The rate of relapse was unaffected; no effect was seen in thirty-one and the eczema became more severe in nineteen. Enclosure of the eczema without ointment to provide "dermatologic rest" was found to exercise a favorable influence in over 50 per cent of the patients. Existing psychic and allergic theories concerning the cure of dermatoses by hospitalization or a change of surroundings might be seen in another light from the fact that the skin may recover also through enclosure and local rest. This type of study is not applicable to weeping or oozing eczemas. Chlorquinaldon (Sterosan) is an oxyquinaline derivative with properties designed to combat infection in pyogenic eczematous dermatoses. A 3 per cent Sterosan concentration in petrolatum and lanolin or a vanishing cream base is available. The sample studied included eighty-nine of 124 patients who had housewives' eczema, nummular eczema, infantile eczema or dyshidrosis. A second group of seventeen patients had pyogenic eczematous dermatoses. Clearing or improvement of the cutaneous lesions was noted by Murphy[162] in 87.1 per cent of all patients. Three patients showed intolerance to the preparation but no case of hypersensitivity was noted. Sixteen

patients with moderate to severe dry contact type eczematous dermatitis were advised by Costello[50] to use Phenergan cream for topical therapy. Fifteen patients were relieved of their pruritus and in most cases two applications a day were sufficient. Patients were not treated over extensive periods of time. Five patients with insect bites obtained prompt relief from itching. One patient with atopic dermatitis and two with neurodermatitis of the hands and arms became worse soon after treatment was instituted. Some of these patients were patch tested and found negative to Phenergan. Furthermore, they could tolerate Phenergan orally. It was concluded that Phenergan cream is helpful in chromic dry contact dermatitis but that nonallergenic dermatoses are unlikely to respond to this agent. In previous publications the reviewer has noted many communications which point to the high degree of sensitization produced by Phenergan cream (Sidi, E.; Melki, G. R.; and Longueville, R.: Dermites aux pommades antihistaminiques. Acta allergol., 5:292, 1952). It has also been shown that cross sensitization exists between Phenergan and chlorpromazine.[231] Other antihistaminic creams have shown a high degree of sensitization on continued use. The lack of sensitization in the study by Costello suggested that most patients used the cream for only a short period of time. One hundred and forty-four patients with pruritic eruptions were followed for eighteen months at St. George's Hospital in London. They had all been treated with hypnosis.[110] Although the results were difficult to assess, the relief of pruritus by hypnosis and simple suggestion was often striking. Chelating agents, particularly calcium disodium ethylenediamine tetra-acetic acid (E.D.T.A.), have been successfully used in the treatment of acute and chronic poisoning by various heavy metals. The subject is briefly reviewed in the *Lancet*[39] which also quotes the work of Maloof[146] who used an ointment containing calcium disodium E.D.T.A. and found it of value against the indolent chrome ulcers seen in the tanning industry.

An across-the-board evaluation of patch tests with various substances on fifty patients with eczematous contact dermatitis, fifty patients with nummular eczema, fifty patients with atopic eczema and fifty normal subjects was made by Wilson.[263] Five hundred tests were made in each group and the author found 6.8 per cent reactions in normal subjects, 15 per cent positive reactions in atopic eczema, 14 per cent in nummular eczema and 23.7 per cent in contact dermatitis. Following careful study, Wilson found it possible to distinguish between a primary irritant and an allergic reaction by retesting after several weeks using serial dilutions of the test substance. A genuine allergic reaction is followed by erythema, edema and small vesicles with strong concentrations of an allergen. The effects diminish gradually as the substance is diluted. The irritant reaction produces erythema and edema, follicular papules or necrosis with strong concentrations, and effects fade off quickly as the test allergen is diluted. Nonspecific false positive reactions occur with dilutions which have no strict bearing on the quantitative relationship to the test and to the strength of the test substance. Irregular patterns in reactivity favor a false positive reaction. It is of interest that repeat tests which were made from one to six months apart were not comparable in every instance. In patients with either atopic eczema or contact dermatitis, reactions which were strongly positive previously are often negative on retesting. It is Wilson's opinion that whatever the test substance, a single positive

test should not be accepted as definite evidence of epidermal hypersensitivity.

Two case reports are recorded by Lewis and Sawicky[132] of nurses who developed erythematous, edematous, scaling, patchy, pruritic dermatitis over the upper eyelids, face, back of the hands and flexures of the forearms. Chlorpromazine was suspected and positive patch tests were found to a dilution of 25 mg per cubic centimeter of this substance. The frequent or long continued contact with chlorpromazine may ultimately sensitize patients. The course of the dermatitis may be protracted. It is well to remember the cross relationships between chlorpromazine and Phenergan.

ATOPIC DERMATITIS

It is known that patients with atopic dermatitis are subject to white dermographism and often are disturbed by sudden changes in temperature. The vascular physiology of patients with atopic dermatitis was investigated by Weber and others[260] by placing the subjects in rooms of various temperatures. It was found that patients with atopic dermatitis had a greater degree of cooling per unit time and a slower rate of warming of the toes and fingers than control subjects (vasoconstriction at the sites). Temperatures of the cubital and popliteal fossae, however, did not react in this fashion but demonstrated a lesser degree of cooling and a faster rate of warming. Patients who did not have atopic dermatitis but were otherwise atopic showed responses similar to patients with atopic dermatitis. The stress associated with change of environmental temperatures produces, in a cold room, a tendency toward decreased vasoconstriction in the cubital and popliteal fossae and increased vasoconstriction in the toes and fingers. The second change noted, in a hot room, was delayed vasodilatation of the toes and fingers and increased vasodilatation of the cubital and popliteal fossae. These studies bear out the clinical impression that relatively small temperature differentials are effective in eliciting abnormal peripheral vascular responses in persons with atopy. It is of interest that this phenomenon reflects purely an abnormality of the contractile elements of the small blood vessels of the skin and has nothing to do with the innervation of these vessels. The white line of dermographism can be obtained equally in denervated areas as in normally innervated skin. The white line can be eliminated by systemic cortisone. A further attempt to elicit more data on the vascular physiology of the atopic individual was made by Russell and Last.[216] The appearance of white dermographism in atopic dermatitis is well recognized. Attempts were made to modify this reaction by surface cold and heat; 1:10,000 solutions of Eserine, atropine, epinephrine, dibenamine, anthisan, carbicol and distilled water were injected intradermally. It was found that subcutaneous administration of xylocaine and procaine block of cervical sympathetics had no effect on the dermographism. Histamine, 1:10,000 intradermally, diminished the effect, and a preparation which was a potent histamine liberator eliminated the effect. It was thought that white dermographism in atopic dermatitis is due partly or wholly to nonliberation of histamine at the sites of trauma or friction, and that the cells had become refractory to this type of stimulus. Davis and Moursund[55] found that the body surface harbors an electrostatic charge which is measurable with an electrostatic voltmeter. Patients with dry skin tend to have higher voltages than those with normal or moist skins, and voltage varies with the relative humidity of the air

as well. Clothing made of wool or nylon will increase surface voltage as does lack of body contact with the ground. Scratching and rubbing of the dry skin causes a significantly greater increase in static charge than does scratching the normal skin. The authors hospitalized a group of patients with atopic dermatitis, exfoliative dermatitis and senile skin in whom pruritus was an important finding. If the patients were grounded, the pruritus improved, especially at night. Control patients were used in whom the wire connection was broken and no improvement in pruritus was noted. The authors believe that in patients with pruritus the improvement noted by the use of baths, lotions and ointments may be related to their minimizing effect on the electrostatic surface charge.

The role of allergy in atopic eczema has been seriously challenged by some experienced and careful observers (Baer, R. L.: Atopic Dermatitis. New York University Press, J. B. Lippincott Co., 1955). Meara[157] studied 112 children with infantile eczema and Besnier's prurigo and compared scratch test findings in forty-three children who had other skin diseases. Sixty-five per cent of the eczema patients had skin positive reactions to one or more test substances, while the control group all had negative reactions. The incidence of positive skin reactions in children over age seven was 90 per cent. Reactions to egg white were found more frequently in children under two and became less frequent in older patients who developed, instead, pollen sensitivity as noted by skin reactions. It is of interest that patch tests to wool in eighty-one children with eczema gave only two doubtfully positive reactions. This is in contradistinction to the findings of Osborne of this country (see below). Desensitization to pollens in six children had no effect on the course of the eczema. It was the conclusion that skin tests in this group do not appear to be related to the severity of the skin disorder or to have any prognostic significance. It is felt that the positive skin test reactions are incidental to the atopic makeup and not of etiologic significance.

The current "polite disagreement" on the subject of atopic dermatitis parallels, to some extent, a similar disagreement in the *British Journal of Dermatology*[63] for 1955. Meara[157] and Russell and Last[216] appear to employ the term of Besnier's prurigo as a synonym for infantile eczema of the asthma-eczema or so-called atopic type. In contrast, Ingram,[111] basing his conclusions on Besnier's original presentation, limits the use of the term to a much narrower group of patients in whom he maintains there is some ectodermal defect separate from, although often accompanied by, an eczematous reaction which he considers of mesodermal origin. In such cases treated with cortisone, the eczematous element may disappear rapidly, but what Besnier calls "lichenization" persists indefinitely. Other ectodermal structures may be affected, and Ingram observed cataracts in 16 per cent of his patients. He believed "an essential nervous and emotional instability due to the disease itself as it affects the central nervous system" exists which also is derived from ectoderm. The whole condition he considered as a "naevoid, a congenital abnormality, probably physiological but possibly structural." It might be argued that Ingram is merely distinguishing the more severe cases of persistent infantile eczema and that there is no real qualitative difference between Besnier's prurigo and atopic dermatitis, a view held by many dermatologists but firmly opposed by Ingram. Following skin tests, elimination of the substance giving the positive reaction had no effect on the course of the eczema which is a well known finding, and few British dermatologists

nowadays place any value on the results of scratch tests in the treatment of infantile eczema. In spite of much evidence to the contrary, Ingram thought that Besnier's prurigo must be regarded as a congenital abnormality of the ectodermal and hypodermal structures. It is difficult to reconcile his findings of ectodermal defect in the light of the presence of urticarial skin responses, passive transfer antibodies, tendency to white dermographism and the vascular abnormalities described by Lobitz and Kierland in atopic dermatitis. Ingram[111] described Besnier's prurigo as a persistent, intractable flexural lichenification with intense paroxysmal itching starting at infancy or early life. Later the whole epidermis is abnormal and thickened with pallor and a dirty earthen hue. The skin is known for its lack of suppleness and markedly exaggerated skin markings. In addition, there are tendencies toward ichthyosis, abnormal pigmentation, either hyperpigmentation or leukoderma. Juvenile cataract in the author's material was found to be present in 16 per cent of patients. He recommended adjustment to the climatic and psychologic environment and elimination of secondary symptoms. Corticotropin, cortisone and hydrocortisone ointment were found to be helpful in relieving exacerbations of the disease.

Tuft and Heck[252] studied 528 patients to determine the relationship between the incidence of horse serum sensitization and previous exposure to this allergen. The findings verified the clinical observation that contact with allergenic agents is extremely important in the induction of sensitization. For example, sensitization appeared more frequently in patients who ate certain foods more regularly and more frequently and in larger amounts than is usually ingested. It is of interest that positive reactions following exposure to horse serum remained for years and it is inferred that a positive reaction may persist for the life of the patient without further or continued exposure to the antigen. The authors advise that allergic patients, especially children, with positive skin test reactions to foods should be advised against eating these foods in large amounts. It is to be noted that in contact eczematous sensitivity to nickel, for example, the continuation or lack of exposure to the antigen did not seem to have an important influence on the persistence of the positive patch test response.

Woodhead[266] stated that in all cases of eczema one can find a disturbed mother-child relationship at a very early level of development. This is the stage before the ego of the child or its personality has had time to develop. Anxiety at this early stage is overwhelming and the resulting psychologic troubles are not psychoneurotic but psychotic. If a mother is neurotic and, in particular, if her hate is repressed and unconscious, the child feels her hostility in her touch, her voice, her holding, however much she is consciously trying to be a good mother. Infantile eczema develops as an attempt to shield the skin from real or anticipated injury from unpleasant and external stimuli and lack of soothing experiences. The mothers of these infants avoid physical contact with them. Bookman[26] discussed the various aspects of atopic dermatitis which he considers the most descriptive term but prefers "eczema," which has more historical support. Again the subject of skin tests in this disorder comes in for discussion and it is believed that all patients with atopic dermatitis, in addition to an adequate history, should be subjected to skin testing. Patch tests in eczema have been tried and discarded by all who have had experience with them. It is stressed that the interpretation of the skin tests is extremely important, and variables such as false positive or

negative reactions or potency of the testing materials can only be assessed by the physician who measures his test results in the light of a detailed history of the case. The author believed that this disorder is not an insurmountable problem if it is regarded as a skin manifestation of allergy intensified by prolonged scratching. Elimination diets are found to be of little value in managing this form of eczema.

It is essential in the study of a chronic disorder that the natural history and prognosis be known. Vowles et al[258] made a study of patients with infantile eczema. Eighty-four patients hospitalized for this disease between 1930 and 1940 were followed thirteen to twenty-two years afterward. Fifty per cent of the patients were personally seen. Two control series were run; interviews were obtained with mothers of fifty-seven patients hospitalized for other diseases who had no record of skin disease and whose ages were comparable to the ages of the patients in the eczema series. A second control group consisted of the school records of 120 children of the same age and sex as those under study. Of the eighty-four patients, six were lost in infancy due to secondary infection. In 55 per cent of the patients, eczema was present up to age thirteen, and in a considerable proportion had persisted to age twenty. Remission in the first three years was seen in 27 per cent. Asthma, recurrent bronchitis or seasonal rhinorrhea was found in 73 per cent of the patients, and in the control group in 5 to 7 per cent. Fifty per cent had asthma alone, and in the control group 2 per cent. Urticaria appeared in 17 per cent of the series and in 1 per cent of the controls. When there was a positive family history of eczema or asthma, a significant increase in the duration of eczema was also found. The eczema persisted longer when there were many children in the family. Response to therapy or the influence of psychosomatic factors was not studied. In a series of ninety-three patients, Purdy (Purdy, M. J.: Brit. M. J., 1:1366, 1953) had previously shown that of fifty-six patients (60 per cent) who had attended the hospital outpatient department with infantile eczema fifteen to twenty-one years previously, 15 to 28 per cent were assessed as having eczema, approximately 30 to 50 per cent had had asthma, 9 to 15 per cent had hay fever and 4 to 8 per cent migraine. Finn[71] sent a questionnaire to patients treated for infantile eczema about twenty years after their previous treatment. Of twenty males, nine reported asthma, five hay fever, ten still had eczema and one had migraine. Of seventeen females, four reported asthma, five hay fever, five had residual eczema and three had migraine. Of the total of fifteen patients with residual eczema, eight had eczema and asthma and seven had atopic dermatitis alone.

Nairn and Anderson[163] studied the lymph nodes of twenty patients with different clinical types of pruritic skin diseases and varying degrees of lymphadenopathy. Two patients in this group had generalized atopic dermatitis. The importance of this work is to demonstrate that the nodes showed hyperplasia of the reticulum cells in the form of pale staining sheets in the medullary part of the nodule. This is considered to be a nonspecific characteristic proliferation of the reticulum cells and should not be confused with the appearance of the lymph nodes associated with serious reticulosis. The same picture was found in generalized exfoliative erythroderma, exfoliative psoriasis and even in an early grave reticulosis. In atopic dermatitis the lymphadenopathy will subside with the control of the underlying condition. Cortes and Monteil[49] reported the case of a twelve-year-old boy with atopic dermatitis who was shown to be sensitive

to chewing chicle. Both asthma and atopic dermatitis were shown to be exacerbated by this agent. A skin test made with 1:100 dilution of the whole chicle extract resulted in a 4+ reaction and an exacerbation of the dermatitis. Positive skin test reactions were also obtained with extracts of chicle, fruit, gutta-percha and gum arabic in 1:100 dilution. Gutta-percha and chicle are both obtained from trees belonging to the Sapoteceae family. There appears to be an antigenic relationship between gutta-percha and chicle. Children who have an active atopic dermatitis have been given poliomyelitis vaccine without any untoward reaction.[190] It is possible that atopic dermatitis may be exacerbated by penicillin if the child is particularly sensitive to this agent. It is present in a very low concentration. The reviewer adds that penicillin-free poliomyelitis vaccines are available.

The admission to hospital of very young children suffering from infantile eczema has been condemned because of the fear of sudden collapse and death occurring during the first few days after admission according to Davies (Davies, J. H. T.: Brit. J. Dermat., 52:182, June, 1940). A case is reported of a five-month-old boy admitted to the hospital for infantile eczema. Treatment was begun with an ointment containing ammoniated mercury and tar. Fifty-six hours after admission his temperature was 104.6° F. and respirations 80. Sixty-eight hours after admission the patient was in severe shock and his temperature was 107° F., the pulse poor in volume and recorded at approximately 172; the respirations were shallow and at the rate of 90. He was given small repeated injections of cortisone followed by oral administration of cortisone and supportive therapy. His condition improved rapidly. A recurrence of a milder form of shock was seen on the ninth day after admission and this, too, rapidly responded to cortisone therapy. It was thought by Marsden and Morgan[149] who reported this case that the shock depended upon an acute adrenal failure. Physicians are warned to watch for a sudden, dramatic improvement in the eczema which usually appears before the general symptoms of collapse occur. The reviewer notes that it has been known by dermatologists for many years that generalized eruptions will appear improved when patients are *in extremis*. Salles-Gomes et al[219] reported the case of a white boy, aged two, who was admitted to hospital with a clinical diagnosis of eczema vaccinatum. Five days earlier his mother had noticed that eczematous patches which had been present in the flexures had become swollen, hot and painful and two days later prurulent vesicles of a herpetic nature appeared in clusters. The patient had never been vaccinated because of eczema but his mother had been vaccinated against smallpox twenty days before his admission and he had scratched one of her vaccination pustules. The lesions were treated locally with soft paraffin and nitrofurazone; otherwise, he had only supportive therapy. Recovery began on the thirteenth day after the onset of the eruption. Eight days later the boy was discharged with only the eczematous patches visible. The vaccinia virus was isolated and identified. The appearance of lesions on the chorioallantois, which has considerable diagnostic value, the behavior on rabbit skin and the cornea and the results of neutralization and immunologic tests completely eliminate herpes simplex virus as the causal agent of this vesiculopustular eruption. Variola virus was also ruled out by the above studies. There are group cross reactions, however, between variola and vaccinia virus when studied by neutralization and immunologic tests. It

is thought that because the lesions appeared simultaneously on the eczematous patches, the agent probably entered the body through the respiratory tract and not through the eczematous lesions. Although recurrent attacks of herpes simplex are very common, reports of subsequent attacks of Kaposi's varicelliform eruption are extremely rare. Feldman and Newman[69] presented three case histories, of a seventeen-year-old white girl, a fifteen-year-old white boy and a nineteen-year-old white boy, all of whom had a background of atopic dermatitis and previous attacks of Kaposi's varicelliform eruption. Recurrences appeared one to two months after the initial attacks. It is known that the recurrent type of Kaposi's varicelliform eruption has a milder and shorter course. Although chlortetracycline was used for treatment, the good effect must be evaluated in terms of the known favorable and short clinical course. The authors favored the name "eczema herpeticum" rather than Kaposi's varicelliform eruption. A further effort to characterize the atopic state with specific reference to the occurrence of cataracts in atopic dermatitis was made by Brunsting et al.[31] Atopic persons are characterized by a high degree of allergic hypersensitivity with the development of atopic reagins in the blood; an exaggerated reaction to various forms of physical and emotional stress; a favorable symptomatic response to steroidal therapy; an exaggerated reaction to infection with the virus of vaccinia and herpes simplex and an abnormal physiologic response in the skin and superficial vascular network to physical agents and to acetylcholine. In addition to this they are prone to the development of cataracts by a mechanism as yet not understood. The opacities can be detected only by slit lamp examination of the lens in the earliest stages. Progression may halt or may continue after the initial finding. It may progress rapidly and this is usually found to occur when periodic flare-ups of the dermatitis appear. Over a thirteen year period, slit lamp examination of the eyes of 1,158 patients with atopic dermatitis revealed cataracts of the atopic type in 136; seventy-nine of the cataracts were either visible or accompanied by subjective symptoms. In fifty-seven the cataracts were detected with the slit lamp alone. Cataracts were unilateral in thirty-nine and bilateral in ninety-seven. The youngest patient was ten and the oldest forty-seven. The dermatitis antedated the cataracts usually by years. One hundred and four of the 136 patients had a history of infantile eczema. About 15 per cent of the patients had symptoms of asthma or hay fever or a close familial history of allergy. X-ray radiation which is frequently used in atopic dermatitis was not considered a cause, since thirty-eight patients who had had no irradiation presented grossly impaired vision because of atopic cataracts in twenty-six.

Leiner's disease is a generalized erythroderma with scaling, usually noted in infants from the fourth to the seventh week. The infants have previously been healthy. The onset is sudden with a generalized maculopapular erythroderma followed by exfoliation. Vesicles and pustules are absent. The scales may be greasy or dry and branny. Yellow, greasy scales confined to the scalp, as seen in seborrhea, almost always are present. Itching is usually absent. Systemic effects may appear later and are usually confined to the gastrointestinal and blood systems. Modern treatment of Leiner's disease includes the use of antibiotics, whole blood transfusions and the topical application of a zinc oxide emulsion with the following constitutents: zinc oxide 6 gm, glycerin 10 gm, olive oil and calcium hydroxide solution, equal parts up to 120. Crotty[53] described the

case of a six-week-old boy with Leiner's disease and anemia. Other than this the laboratory findings were normal. Severe diarrhea appeared one week after admission, in spite of administration of penicillin and high vitamin supplements, and transfusions of whole blood. Streptomycin intramuscularly as well as antidiarrheal measures were successful in improving the gastrointestinal condition. The calcium hydroxide emulsion was the only local treatment used. An excellent table with a differential diagnosis is presented.

As in considerations of the pathogenesis of atopic dermatitis, desensitization of the atopic skin is a subject of great controversy. Most, if not all dermatologists have great skepticism in this regard; allergists, however, have been building up a fund of laboratory and clinical data suggesting that this is a possibility. Tuft[251] found that sensitivity to house dust is harder to determine in dermatitis than in asthma because skin symptoms may be delayed for twelve to twenty-four hours. It is likewise difficult to outline the role of wool which may act as an inhalant, contactant, allergen or aggravate the skin by nonspecific irritation. The incidence of positive skin reactions to wool was 63.2 per cent in his series. It is Tuft's opinion that a consideration of inhalant allergens is essential to clinical management, especially in older children who are not improved after removal of food allergens. He supported the specific allergenic management of these patients, using subcutaneous and intracutaneous injections and varying the concentration of the extracts depending upon the patient's response locally and the skin response generally. Another champion for desensitization, and this time a dermatologist, recorded experiences with allergic dermatitis produced by inhalant molds. In a study of 1,000 patients with eczema, Jillson and Adami[118] found that airborne molds were the causal allergens in about 1 per cent of patients. The mold counts for Hanover, New Hampshire for an eighteen month period are presented. Peaks are seen in the fall from decaying leaves and sharp drops in mold counts are noted when there is complete snow coverage of the ground. Frost does not affect molds as it does ragweed pollen. A typical case is presented of a thirty-six-year-old woman with a dermatitis of the hands of ten years' duration. She had a background of infantile eczema and hay fever from the age of twelve to sixteen. A mold skin test became positive in forty-eight hours as shown by delayed papular reaction, and this was accompanied by a flare-up of the dermatitis of the hands. The patient was "desensitized" with a composite mold antigen, using 0.1 cc (1 protein nitrogen unit per cubic centimeter) subcutaneously twice weekly. Clearing resulted in five months' time and the hands were completely clear in nine months. A two-year follow-up showed no recurrence. In a similar fashion, Storck had noted acute recurrences of dermatitis of the head, neck and extremities of patients which did not correspond to direct external contact. Some of these recurrences were traced by Storck[241] to inhalation of various allergens. Dermatitis from the inhalation of penicillin and chlorpromazine was noted in five nurses. Patch tests were positive in all. Dermatitis resulting from inhalation of turpentine fumes was observed in four patients and suitable patch tests were positive in all four patients. A patient noted that there was swelling and erythema of the eyelids during cherry blossom time and also noted that intensive itching occurred after ingestion of cherries. Five patients with an eczematous eruption resembling disseminated neuro-

dermatitis traced recurrences to inhalation of dust. Scratch tests with house dust were positive. To support further his contention of the role of various allergens inhaled by patients, it was shown that Prausnitz-Küstner tests were positive when the test allergen was introduced into the nostrils of normal control subjects. The reviewer notes that although most cases of sensitivity to ragweed oil are probably due to contact with the stems or leaves of plants, airborne ragweed may cause flare-ups in allergic eczematous contact type dermatitis by inhalation of ragweed pollen.

Intra-uterine exposure to an allergen in the diet of a pregnant mother of a potentially allergic infant is still a controversial subject. Glaser[89] took the positive side of this controversy and pregnant mothers are instructed by him to avoid eggs and foods containing egg. They are given each day one pint of milk which has been boiled for ten minutes. Cheese is omitted. Meat is the chief source of protein, and calcium and phosphorus are added to the diet. It would appear that if egg is eliminated from the potentially allergic infant, at least to the age of nine months, some type of protection against egg sensitization is developed by the infant. Human breast milk is preferred for the infant. If this is not available, soy bean milk or a substitute for cow's milk is preferred. By carefully following ninety-six infants on this type of regimen it was found that in a control group the incidence of allergic disease in potentially allergic children started on cow's milk from birth was almost four times that of children started on soy bean milk. It is believed that the progressive increase over the years in the relative frequency of allergic diseases in children can be explained at least in part by the gradual abandonment over the past twenty to thirty years of breast feeding by mothers. O'Keefe[168] reported the relation between a careful dietary study and cortisone therapy in the treatment of infantile eczema. Before therapy is begun, a carefully detailed dietary history is essential. The infant is then given cortisone therapy in dosage sufficient to clear up most but not all of the dermatitis. Some of the skin lesions are left to serve as an index of further improvement. Exclusion of the suspected food from the diet should result in the disappearance of the last residuals of the eczematous eruption. Further confirmation of the diagnosis may be obtained by then resuming the suspected food in the diet and noting a return of the residual lesions. When the infant is in remission and under proper dietary control cortisone may then gradually be discontinued. O'Keefe found that it is possible to introduce the incriminated food gradually in small amounts in the child's diet without a recurrence of the eczema.

Three patients with severe intractable neurodermatitis are described by Tilley and Barry[250] who were given chlorpromazine with at least temporary relief of itching. These were patients in the age group of forty to sixty years who were hospitalized for their dermatitis. Since all previous measures had been failures, the patients were given chlorpromazine, 50 mg, intramuscularly three times daily. This was continued for one week, and later the drug was given by mouth, 50 mg, four times a day. Relief of itching was seen within twenty-four hours; restlessness and overactivity were diminished. Excoriations, scaling and lichenification slowly subsided. The patients improved rapidly and as a rule were dismissed at the end of ten to fourteen days. One patient, however, developed phlebothrombosis which required surgical attention. Some of the physiologic actions of

chlorpromazine include the reduction of body temperature, which is accompanied by ischemia of the skin and reduced capillary permeability. The main effect is a soporific action that tends to promote sleep. Tilley and Barry advised that the use of chlorpromazine in neurodermatitis be limited to patients who are hospitalized and can be kept under careful supervision. The tranquilizing drugs Serpasil, Thorazine, and Equanil are in popular use today for many dermatoses which have psychosomatic overtones. One of the first studies reported is that of Rein and Goodman.[202] Nineteen patients with atopic dermatitis and eighteen patients with lichen simplex chronicus were given 0.25 mg of Reserpine four times daily for one month. Placebos were given for an additional month to some patients. About 80 per cent of the patients experienced a definite relaxation, tranquilization, sedation and lessening of inner tension. Side effects included nasal congestion, increased appetite, depression, dreams, nocturia, dyspnea, weakness and nausea. Although the systemic effects were satisfactory, topical therapy was necessary to produce local improvement of the skin. It is the general experience that Reserpine by itself does not improve common dermatoses in spite of the tranquilizing effect. Ferrara and Pinkus[70] used Alseroxylon (Rauwiloid) on 436 patients with various dermatoses (atopic dermatitis, disseminated and localized neurodermatitis and others) in which they felt that a psychosomatic factor was contributory or causal. Rauwiloid is a concentrate of active alkaloids extracted from the root of Rauwolfia serpentina. Treatment was given for two to six weeks and controls in the form of placebos were used in some patients. Dosage of Alseroxylon was 4 to 8 mg per day. The course of all patients was carefully followed at weekly or biweekly intervals. Tranquilization was noted in all patients. Pruritic dermatoses were improved in varying degrees from 50 to 100 per cent. It was the opinion that the tranquilizing action of the drug was helpful in the management of pruritic dermatoses.

Combes and Reisch[47] studied the antihistaminic properties of a new piperidine compound (Sandostene) alone and in combination with calcium gluconate intravenously in 135 patients suffering from various dermatoses associated with pruritus and insomnia. Sandostene was given in compressed tablets, each containing 25 mg of the active ingredient; dosages varied daily from 75 to 250 mg. Those patients treated with calcium gluconate received 10 cc (Neo-calglucon) plus 0.05 gm of Sandostene. One patient received intravenous medication once daily for thirty-seven days. Best results were obtained in disseminated neurodermatitis (atopic eczema) and contact dermatitis, especially of a generalized type. The preparation was administered orally to 110 patients, of whom eighty reported excellent to good results and thirty reported doubtful results or failure. Sandostene plus Neo-calglucon was administered intravenously to twenty-five patients, of whom twenty-one reported excellent to good results and four doubtful results or failure. There were no instances of toxicity and the combination was well tolerated. Detailed topical therapy for allergic dermatoses was described by Haeberlin.[98] It was suggested that antihistaminics and anesthetic agents should be avoided in this group of patients. Topical steroid therapy was mentioned briefly. Other factors besides local treatment which must be considered are psychogenic factors, general health, local irritating factors, local infection, and allergic factors. The internal use of antihistamines has been disappointing except in some cases of

urticaria. The internal use of steroids is falling into disfavor in cases which may run a protracted course. Steroids are usually avoided in cases of atopic eczema since increasing doses may be required for indefinite periods and serious late effects encountered. In a paper on the art of dermatology, MacKenna[141] wisely counseled on the management of dermatologic patients who have a functional background. Much of his discussion can well be applied to the management of patients with atopic dermatitis. It is important to recognize the markedly obsessional or conscientious individual who produces a pencil and a notebook as soon as treatment is discussed. This type of patient jots down everything the physician says and even makes notes on the prescription slip when he takes it from the physician. If this patient is instructed to "clean off the last application of ointment with oil before applying the next layer of ointment," he will traumatize his skin vigorously each time he changes the dressing by conscientiously scrubbing away with a swab soaked in oil to remove every particle of zinc before he applies the ointment. This patient will fail to get well not because of poor management but because of his personality characteristics.

Epstein[66] noted that infection or bacterial invasion plays a major role in some eczematous dermatoses, contact dermatitis as well as atopic and seborrheic dermatitis and especially in bacterial eczemas. It was found that hexachlorophene (G-11) is a nonstaining, inexpensive antiseptic with a low sensitizing index. Hexachlorophene, 1 to 2 per cent, can be added to zinc oil, sulfonated bitumen paste or in buffered solution of aluminum acetate in a hydrophilic base. *In vitro* tests showed hexachlorophene bacteriostatic against *M. pyogenes* var. *aureus* and hemolytic streptococci. The growth of two strains of *Ps. aeruginosa* was not inhibited by hexachlorophene. The agent was well tolerated and only one case of true contact sensitivity was found in several hundred patients. Patients with atopic dermatitis are often advised to seek climatic change in such places as Florida, Texas, the desert areas of the United States, or southern California. Studies were made by Klüken[121] on climatic effects on atopic dermatitis using skin temperatures of finger tips recorded with thermocouples in patients before and after climatic changes were made in their living. Control studies were also made. An increase of cutaneous temperature after a climatic treatment could be demonstrated and was more marked in children with normal skin than in those with exudative eczematoid skin. Interpretation of these findings coincides with the clinical observations that children with atopic dermatitis usually have pale, comparatively cool, clammy skin (poor circulation) and respond well to fever therapy, ultraviolet or x-ray radiation, all of which tend to improve the circulation of the skin. Placental extracts used concurrently, parenterally and locally to treat nurslings with seborrhea sicca and eczema gave good results especially in infants with the first condition according to Santyan y Velasco and Amore.[223] Placental tissue in placental juice was used for the parenteral route; placental powder incorporated in 50 per cent oily vitamin medium was used for local treatment. Twenty-six infants were studied and a control group having the same conditions was also observed. Treatment was continued for from fifteen to thirty days and tolerance to the preparations was good. Four of the eczematous children made a complete and definitive recovery, three improved and in five the condition recurred after initial improvement. Pruritus seemed to be very well controlled. Clear-cut remissions were never observed in the controls. The mechanism of

action of placental therapy in these conditions is still obscure. Gonadotropin and estrogen type endocrine substances were removed from the placenta in processing so that improvement could not be attributed to these agents. Studies on the mode of action are in progress.

URTICARIA

Five hundred patients suffering from urticaria were studied by Steinhardt.[240] This complaint was most common in patients in the third and fourth decades and was more frequent in women, probably due to possible psychic factors, medications during childbearing age, and to pelvic infections and endocrine imbalance related to pregnancy and menopause. Food allergy was suspected in 30 per cent of the patients with chronic urticaria. Seventeen per cent improved when the suspected food was removed. This food did not prove to be an exotic or rare food but rather an everyday, staple food. Drugs were found to be causal in 17 per cent of patients. On closer study of patients seen after 1948, it was found that this percentage had increased to 32.5. The latter increase was thought to be due to allergy to penicillin. In the first group of 300 cases studied from 1942 to 1947, psychologic factors were causal in 15 per cent. This figure became 40 per cent in the second study of 200 cases from 1948 to 1953. Urticaria traced to infections was present in 14 per cent of patients. Cholecystitis, appendicitis, infected teeth or tonsils, chronic prostatitis, cutaneous infection and parasitic infestation were the commonest causes. Physical and contact allergies were present in 3.3 per cent in the first group up to 1948 and in 10.5 per cent in the second group. The cause was undetermined in about 40 per cent of the patients in the first period and 14.5 per cent in the second period. Angioedema during the course of urticaria was present in about half of the patients. Blood eosinophilia was of no diagnostic importance. Antihistamines seemed to relieve pruritus in 78 per cent of patients and the temporary use of ACTH or cortisone appeared justified in serum sickness of moderate or severe degree.

From time to time cases have been reported in which urticaria has accompanied a paroxysm of malaria and has disappeared following the administration of antimalarial drugs.[12] It has been suggested that this is an allergic phenomenon due to infestation with malaria parasites, analogous to that which occurs in hydatid disease. Thomas and Rideout (Navy Med. Bull., Washington, 29:470, 1931) described a case of vivax malaria in which the initial paroxysm was accompanied by giant urticarial wheals, covering the entire body and extremities, and considerable edema of the glottis. Symptoms cleared following the administration of quinine but reappeared with the second paroxysm. Symptoms were then controlled by epinephrine. Hollander[109] reported a sixty-six-year-old executive who presented an acute painless swelling of the left side of the lower lip which began sometime during the night. This subsided the next day. The patient recalled that before retiring he had smoked a filter tip cigarette, probably for the first time. Repetition of this experience again resulted in a peculiar sensation of fullness in the lower lip and shortly afterward a recurrence of the swelling. This was again repeated with the same result. The case is reported of a forty-five-year-old man who developed patchy erythematous areas often associated with giant hives.[186] Symptoms were partially controlled by steroids but they promptly recurred when cortisone

therapy was terminated. It was thought that the fleeting erythemas develop when the concentration of liberated histamine is so low that only the first phase of the triple response of Thomas Lewis (the local vasodilatation) develops. Geometric patterns may be seen from the diffusion of histamine to the periphery with the corresponding development of refractoriness in the center of the lesions. This pattern is most frequently seen after drug injections. Intensive investigations may frequently end in fruitless search, so the patient should be treated symptomatically in the hope that a spontaneous remission will occur.

Benjamin et al[20] reported the case of a forty-year-old white man who presented an allergic contact dermatitis due to a whealing agent which releases histamine "drug 48/80." A wide variety of chemicals are known to be capable of releasing histamine from the skin without producing any evidence of cell damage. These agents include morphine, codeine, 5-hydroxytryptamine (serotonin), stilbamidine, and most potent of all "48/80." Although the early injections of "48/80" produced a marked local histaminic reaction with pain, pruritus, erythema and whealing, ultimately similar introduction of this antigen produced a dermatitis of the contact eczematoid type. This followed regularly the intradermal as well as the iontophoretic introduction of the preparation. Patch tests made on this patient with a screening tray of known sensitizers were negative. The reviewer recalls a ten-year-old girl in whom a severe local reaction to a ragweed injection developed during the course of routine hyposensitization for hay fever. This intense erythema was followed by an eczematous reaction localized to the site of injection.

Urticaria was reported in an infant five months of age; a generalized urticarial eruption developed after the second monthly dose of alum-containing diptheria-pertussis-tetanus vaccine.[195] It was the opinion that urticarial eruptions as a result of these toxoids are very unusual. It was suggested that instead of the triple vaccine, the individual members be given separately. For pertussis, instead of alum-precipitated vaccine, the saline pertussis vaccine could be selected and a 0.1 cc of vaccine containing 15 to 20 billion organisms per cubic centimeter should be injected subcutaneously. If no reactions occur, this injection should then be followed by larger doses at seven to ten day intervals. A similar plan would be adopted for diphtheria and tetanus, using plain toxoid. It was stressed that the outside of the needle should be free of any material used for injections so as to avoid contamination of the skin and subsequent sensitization. More than one injection should not be made in the same locality. Three patients with an interesting type of bullous lesion associated with urticarial papules were reported by Van der Meiren[257] and Achten. Dermographia and marked pruritus accompanied the condition and two patients had a personal history of urticaria with a causal food background. The characteristic features of this condition are a history of allergy, an eruption of short duration and blisters associated with urticarial lesions. Dermographia, itching and lesions of a similar type help to differentiate the disease from dermatitis herpetiformis which is a polymorphous eruption. The study of the condition histologically suggested that mechanical factors such as physical tension and progression of the liquid into the epidermis were responsible for the blisters. The occurrence of urticaria, angioneurotic edema, various toxic eruptions and herpetic eruptions during pregnancy has always been a problem in management. In response to a query, it was difficult to decide on the cause of skin reactions in a

patient, gravida V, Para III, aged thirty-seven, who had recurrent hives postpartum and in addition developed a generalized eczematoid dermatitis.[184] It was thought that the hormones produced by the placenta may be responsible, in which case there is no prophylactic therapy. Drugs given at the time of delivery should be considered. Foremost, however, is hypersensitivity to either placental products or to the patient's milk. The latter two conditions are exceedingly rare. Instances of urticarial types of reactions at times accompanied by arthritic symptoms and signs and general glandular enlargement have developed in patients who have received penicillin by the parenteral route and have recurred despite therapy with cortisone or the antihistaminics for a period of several months.[189] It was evident from the description given that the patient was suffering from a reaction of this general type. These reactions have occurred following the use of amorphous penicillin, crystalline penicillin and procaine penicillin as well as benzathine penicillin G. There is no statistically controlled evidence that inoculations of vaccine virus are of prophylactic or therapeutic benefit relative to the occurrence of these allergic reactions. As far as it is known, the recurrent bouts of urticaria disappear although it may take a number of months before they disappear completely. Patients who have had such severe reactions should be warned against ever having penicillin injected again.

Investigations into the pathogenesis of urticaria due to cold were made by Kölbl and Wolf.[122] A case was reported of a boy of eleven whose mother had severe asthma. He suffered for two years from urticaria after exposure to cold, skiing and swimming. It was noted that the eosinophil count rose from 2 to 8 per cent after exposure of large skin areas to cold. Prausnitz-Küstner reactions were positive in the serum taken after exposure to cold and negative after pressure or exposure to heat. ACTH controlled his urticaria and oral antihistamine treatment and autodesensitization (daily cold hand baths for one to two minutes) controlled the cold urticaria. A second case presented was that of a boy of thirteen with a negative family history of allergy, who suffered for ten years from urticaria due to cold. Local exposure to cold water or ice caused no reaction, but after prolonged walks in cold weather, urticarial lesions with red halos and intense pruritus appeared. This subsided after he returned to a warm room. The eosinophil count (3 per cent) was unchanged by exposure to cold and Prausnitz-Küstner reactions were negative. Relief was obtained by oral antihistamine treatment and desensitization by gradually increasing exposure to cold. Although the mode of production of the urticaria was the same in both cases, the author thought that the first case was an allergic basis and the second case might be one of vasoneurotic origin. It is assumed that histaminic substances are significant in the pathogenesis of urticaria. In studying urticaria due to ultraviolet, Porter[180] made tests with a special dielectric filter and by projection of spectral bands found that sensitivity extended from the ultraviolet region throughout the visible spectrum into the infrared. It is believed that the response is due to an allergic mechanism. Light waves are absorbed by certain cells in the skin so that they become sensitized. On subsequent exposure a reaction occurs leading to a release of H substance. Passive transfer antibodies to light were absent in this series of patients sensitive to 4000 to 5000 Å. Passive transfer antibodies are usually found below 3700 Å. A group of diseases due to photo-

sensitivity which range from urticaria to cancer can be prevented in some instances. The active spectrum of sunburn erythema lies between 2900 and 3170 Å. Compounds that possess the physical property of absorbing energy in this range have been investigated for their advantage in preventing sunburn. It has been found that ointments incorporating 15 per cent para-aminobenzoic acid and one containing 5 per cent cycloform (isobutyl para-aminobenzoate) offered excellent protection. Downing[60] preferred the followed preparation: Tannic acid 6.0, salol 1.0, castor oil 5.0, water 5.0, and alcohol 83.0. It is suggested that para-aminobenzoic acid can be used in a vanishing cream base using 15 per cent of the active ingredient. Light sensitivity victims can be protected by the use of chloroquine diphosphate which has a similar structure to quinacrine (Atabrine).

The classification, pathogenesis and management of acute and chronic urticaria and angioneurotic edema are described by Fromer.[83] Histaminic and cholinergic types of urticaria are differentiated. Management depends largely on etiology. Antihistamines and steroids are most useful, although the latter may prove to be disappointing in some forms of urticaria. Clein[42] discussed therapy of various allergic manifestations with a new antihistamine, Sandostene, 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate. This is available in 25 mg tablets; syrup, each 4 cc containing 12.5 mg of antihistamine and the equivalent in calcium ion content to 1 gm of calcium gluconate; ampules, each 10 cc containing 50 mg of Sandostene in 10 per cent solution of calcium gluconogalactogluconate. The preparation has been used to some extent in clinical research and is reported in the European literature. Clein reported 124 patients treated with Sandostene alone or in combination with calcium orally and intravenously. The intravenous form of the product plus calcium was used in severe urticaria in combination with angioneurotic edema. There were four patients with urticaria and seven patients with angioneurotic edema and urticaria among the group of 124 patients. There were seventeen children with eczema. Three of the four patients with urticaria were relieved, and five of the seven patients with urticaria and angioneurotic edema were improved. Of the seventeen patients with atopic dermatitis, eight obtained moderate relief and nine were not improved. In the entire group, two patients had toxic manifestations of minor significance. Laugier[128] used sedation in patients with generalized eczema and prurigo, and suggested its further use in urticaria, psoriasis, leg ulcers and in skin diseases in which there are psychosomatic implications. Trianol, Somnifen, combinations of various barbiturates, amytal and chloral hydrate were the agents used. Although doses vary in different patients, the general idea is to produce prolonged sleep and to allow waking intervals not to exceed one or two hours. The patient is placed in an absolutely quiet, airy, darkened room. Constant observation by trained personnel is necessary. The patient is watched very carefully so that accidents are exceedingly rare. Cardiovascular collapse and hyperthermia have been reported. The treatment has limited application because of the cost and time loss involved since a trial of from ten to fifteen days is necessary.

DRUG ERUPTIONS

Barr[18] stated that the multitude of new and relatively untried diagnostic and therapeutic procedures, which form an integral part of the practice of medicine today, recalls the admonition "Be sure you do no harm." Diagnostic methods, formerly simple, are becoming increasingly complex and formidable. Therapeutic preparations are confusingly numerous and varied. In the lists of 1953, more than 140,000 medicaments were available to practitioners, and 14,000 new preparations were added during the year. It has been estimated that 90 per cent of drugs now in common use have been introduced within the last twenty-five years. Sudden death may follow the intravenous administration of such a relatively inert substance as dehydrocholic acid (Decholin). Coryza, bronchospasm, conjunctival inflammation, allergic eruptions, thrombocytopenic purpura, fever, shock, cardiovascular collapse and death have followed the use of as common a drug as acetylsalicylic acid. It is estimated that 100 to 200 acute anaphylactic-like reactions occur from penicillin yearly. The author again called attention to the well known reactions following the use of penicillin and the broad spectrum antibiotics, phenylbutazone and chlorpromazine. In addition, a number of reactions to Apresoline are recorded, and it is noted that this drug can render patients photosensitive in addition to producing erythematous eruptions. The various problems concerned with the definition, mechanism and reporting of drug allergy were described by Brown.[29] Allergic reactions are distinguished from purely toxic, idiosyncratic, intolerance and other side effects. All the details of possible mechanisms are explored in this stimulating article. It is pointed out that relatively few of the large number of case reports of drug reactions are sufficiently detailed to be of value. Furthermore, there is often a discouraging delay in reporting reactions to new drugs currently in vogue. Anyone planning to report a drug reaction will profit from the study of this contribution.

Allergic reactions are among the most frequent side effects associated with the use of modern drugs. There has been an enormous increase in the use of drugs. The character of the new drugs influences the incidence of drug sensitivity. New preparations seem to be powerful remedies and it is known that substances of greater chemical reactivity are strong sensitizers and may produce allergic side reactions more frequently than substances of low reactivity. Mayer[155] investigated the various experimental procedures available for establishing the absence or presence of sensitizing properties of new drugs. Two most important forms of allergic side reactions produced by drugs include the sensitization of the mesodermal cell apparatus affecting the cells of the capillaries and the bronchi as well as the smooth muscle of the intestine and the glandular system. This is the immediate or anaphylactic type of sensitization. Drugs producing this type of reaction are proteins, substances of high molecular weight, compounds which form colloidal solutions and many simple compounds of low molecular weight which readily combine with proteins. The second important form of allergic drug reaction involves the sensitization of the epidermal apparatus. This is designated as eczematous, contact or delayed type of sensitization. The shock organ is the epidermal cell and contact is usually made from outside the body. Many drugs, however, produce this same type of reaction from within, after absorption through the stomach or after subcutaneous or intravenous injection.

Compounds most frequently responsible for contact type are simple chemical substances of low molecular weight. It is to be noted that certain authors distinguish the tuberculin type of sensitivity from the contact type. Allergies against certain drugs, notably arsphenamines, may present the same form of reactivities and are, therefore, considered as tuberculin type. The shock organs involved in the tuberculin type of reaction differ from the contact type of hypersensitivity. The principal site in the tuberculin type is the cutis as in atopic sensitization, but at the same time the epidermis is strongly involved as in the contact type. Experimental sensitizations in animals producing epidermal sensitization are readily elicited in guinea pigs after cutaneous or intradermal application of drugs known to be strong sensitizers for man. Examples of these are primulin, poison ivy extract, aromatic amines such as paraphenylenediamine, nitro compounds, nitroso derivatives, picryl chloride, chlorobenzene, phenylhydrazine and a number of others. Anaphylactic sensitization of guinea pigs with drugs and substances of low molecular weight chemically combined with proteins have been induced, but not regularly. It is not possible to imitate in animals a great variety of allergic reactions observed in man. In many instances there seems to be no distinct correlation between experimental allergies and those that occur naturally in man. Man can be experimentally sensitized with the preparations previously described for animals. All attempts to produce experimental atopic sensitization in man with simple chemical compounds have failed. If a substance sensitizes the skin of guinea pigs readily and strongly then it may be inferred that it is not proper to use this compound as an external remedy. It may, however, not produce untoward allergic symptoms when administered by mouth. Although man is readily sensitized, it is not wise to use human beings for tests of experimental hypersensitivity. Numerous important and unexpected cross sensitizations occur. The voluntarily sensitized person is endangered for the rest of his life since it is well known that natural and artificial sensitizations persist for long periods and probably for the duration of life. A great deal of further work is necessary in devising methods that will permit the assessment in a routine manner of the allergenic propensity of a new drug intended for human consumption. The incidence of fixed drug eruptions in a large hospital practice with over a half million admissions was studied by Cornbleet et al.[48] The fixed eruption is limited to one or more isolated areas of involvement. It usually appears eight to twenty-four hours after the oral or parenteral administration of the causative agent. The earliest manifestation is erythema and itching, and this is soon followed by hyperpigmentation with subsequent involution of the lesions if the further ingestion of the allergen is discontinued. After the eruption subsides, a subsequent administration of the drug causes a flare in the previously involved sites. Agents in common use which have been known to produce fixed eruptions include the coal tar derivatives, arsenicals, barbiturates, belladonna, bromides, chloral hydrate, digitalis, ephedrine, iodides, magnesium hydroxide, opium and its alkaloids, phenolphthalein, quinine, salicylates and sulfonamides. It is of interest that in addition to drugs, serums, vaccines, alcoholic liquors, karaya gum and certain food (lentils, tomatoes, and others) have been known to produce a fixed type of eruption. Fixed eruptions have also been reported following the use of the modern antibiotics, chlortetracycline and oxytetracycline. The incidence of fixed drug eruptions is exceedingly low and the set of figures presented by the authors

indicates an incidence rate of 0.0015 per cent. This represents a total of nine cases in well over half a million hospital admissions. Franceschini[76] studied 613 patients with bronchial asthma who were seen in the outpatient department of the University of Rome allergy clinic between 1952 and 1955. Studies were made to determine the incidence and type of clinical hypersensitiveness to various medications. Fifty-one of 613 patients (8.32 per cent) showed clinical hypersensitiveness to drugs. Almost 4 per cent of patients were hypersensitive to acetylsalicylic acid. Hypersensitiveness to aminopyrine and its derivatives was the next most common. Clinical manifestations of intolerance were urticaria, bronchial asthma, angioneurotic edema, serum sickness, erythema, purpura and fever. Scratch tests with drugs were negative except in one instance in which a patient showed a positive reaction to acetylsalicylic acid.

It can be shown that the thrombopenic index may be used as an indicator of an allergic reaction in man. This is of interest because the thrombocytes may be reduced from 15 to 40 per cent in peripheral blood ninety minutes after exposure of the patient to an excitant. Normal individuals show only slight variations in the number of thrombocytes. Storck[242] studied more than 200 patients with many different forms of drug allergy and showed that the thrombocytopenic index is both reliable and specific. One must have a technician who is experienced in counting thrombocytes by means of a phase microscope, and it is important to remember that certain drugs such as histamine and epinephrine have an effect on the thrombocyte count without any reference to sensitization. *In vitro* studies show that thrombocytes are agglutinated when an allergen is added to oxalated blood. There is a direct relationship between the agglutination index and the decline in thrombocyte level in allergic individuals. With this method it is thought that it is possible to obtain a specific diagnosis especially of a drug allergy without risk of exposing the patient. In addition, Storck[243] and others reported at the International Symposium in Basle, July 3 to 8, 1955, on a new serologic method of identifying allergens. They had shown previously that an allergen added to a sensitized serum would cause conglomeration of platelets. They now showed, using a sensitive nephelometer, that adding an allergen to a sensitized serum causes turbidity at certain dilutions of the allergen. They found two causal factors: one which dialyzes through "cellophane," and a nondialyzable, nonspecific factor which is present in the serum of guinea pigs, cows and horses but absent from that of rats and rabbits. The reviewer notes that if this method proves trustworthy it will help solve the problem of drug sensitivity in a patient about to receive a sensitizing drug.

Among the substances of low molecular weight, phenylhydrazine is one of the strongest skin sensitizing agents known. A number of hydrazine derivatives are used in medicine and one of these is Apresoline, a hypotensive agent. Mayer[156] and others were able to sensitize guinea pigs experimentally using 0.1 ml of 0.5 per cent aqueous solution of 1-hydrazinophthalazine. Three intradermal injections of three sites were given on alternate days. On the twenty-first day following the first sensitizing dose the animals were challenged intradermally on the opposite shaven flank with 0.1 ml of 0.5 per cent solution of 1-hydrazinophthalazine. The challenged sites flared with a typical delayed tuberculin type reaction and there were fifth and seventh day flare-up reactions such as have been observed in sensitization experiments with neoarsphenamine. No

whealing reactions were noted. Cross-sensitization reactions were possible with substances chemically related to 1-hydrazinophthalazine. Inhibition of dermal sensitization by prior feeding of the sensitizing agent was possible. This was first shown by Chase in experiments with picryl chloride and 2,3-dinitrochlorobenzene. From the ease with which sensitization occurred to this preparation, Mayer speculated that a similar sensitization to 1-hydrazinophthalazine or its analogues may occur in men following therapeutic use. It is known that substances with strong skin sensitizing properties for humans are also powerful sensitizers for the guinea pig, especially primulin, phenylhydrazine, paraphenylenediamine, dinitrochlorophenol, trinitrotoluene and amino azodyes. Contrary to the ready sensitization of the guinea pig with 1-hydrazinophthalazine, however, skin sensitization in patients arising from its use has been, thus far, exceedingly low. Within the past year, of a total of an estimated 400,000 patients treated with this agent, only ten cases of dermatitis medicamentosa which could be associated with the delayed type of sensitization have appeared. The route of administration of an antigen is a strong factor in determining the number of sensitizations. Procaine, for example, is a strong contact allergen and is responsible for a great number of skin sensitizations among dentists, but when used subcutaneously as a local anesthetic the incidence of sensitization is much smaller. A substance which regularly leads to sensitization of the epidermis when used topically will predominantly produce asthma when inhaled as it occurs with paraphenylenediamine, penicillin, neoarsphenamine and quinine. Any skin sensitizing experiment with prospective drugs must be interpreted with great care. One must consider not only the intrinsic allergenic nature of the compound but also its proposed clinical use and route of administration. It is of interest that efforts to produce in guinea pigs such allergic side effects as the Nirvanol-disease or the usual anaphylactic reactions with penicillin have been fruitless.

Fromer[80] discussed anaphylactoid drug reactions from the standpoint of recognition and management. Bromsulphalein, Decholin, procaine, iodine-containing contrast media and penicillin reactions are described in some detail. Successful management of these emergencies is based on preparedness to meet the emergency. Kits containing a tourniquet, epinephrine ampules (1:1000), sterile syringes, intravenous aminophylline, Benadryl for injection, stimulants and intravenous hydrocortisone should be at hand. Suction and intubation equipment with an operator qualified in the use of this equipment may be life saving. Oxygen should be easily available in small, portable, easily operated units. Finally, it should be remembered that the use of plasma and intravenous steroids may be necessary to combat the delayed reactions that may occur. Clark[41] reported success by giving sodium bicarbonate and potassium bicarbonate in various proportions and amounts to patients with acute or chronic allergic manifestations. Five grams of combined alkalis dissolved in water is given every hour or two for one, two or three doses, particularly in acute cases of allergic reactions. The intravenous injection of sodium bicarbonate has been particularly helpful in severe allergic reactions to penicillin. The solution used is available in an ampule containing 3.75 gm of sodium bicarbonate in 50 cc of water. The author also used one sixth molar sodium lactate. The lactate should be used with caution, however, particularly in patients who have cardiorenal, hypertensive or arteriosclerotic diseases.

Many substances including pentose nucleotide, pyridoxine, folic acid, liver extract and ACTH and cortisone have been used in the treatment of agranulocytosis following drug therapy.[10] There is no convincing evidence, however, that any of these remedies has a specific effect in stimulating leukopoiesis under these circumstances. The transfusion of leukocytes is likewise of little or no value. Fortunately the progression may be stopped by omitting the drug in most cases. Prognosis can be assessed by marrow puncture. The outlook is more serious if the red cells as well as the white cells are depressed.

Antihistamines.—In France, it was found that 50 per cent of all eczemas of therapeutic origin seen by Sidi et al in 1953 were due to Phenergan cream.[231] Once sensitized, the subsequent oral administration of Phenergan usually leads in four to five hours to a rise in temperature followed by reactivation of the dermatitis within twenty-four hours. In addition, the patient who is allergic to Phenergan usually becomes allergic or intolerant to regular daylight, and the allergy may last for years. This may explain the appearance of a chronic erythematous or dusky colored dermatitis with dryness of the skin, fissuring and slight scaling on exposed areas. Some of the Phenergan allergic individuals were also sensitive to other substances. Out of 128 patients, 30.7 per cent reacted to paraphenylenediamine. Some were sensitive to the procaine series and sulfonamides. Hematologic reactions caused by antihistaminic drugs are rare.[181] Agranulocytosis has been described in a few instances following administration of tripelennamine (New England J. Med., 241:865, 1949; J.A.M.A., 143:741, 1950; J.A.M.A., 142:447, 1950) and Phenergan. There is one case report of aplastic anemia occurring in a sixty-five-year-old man who had taken tripelennamine and pyrilamine (J. Maine M. A., 46:83, 1951). Hemolytic anemia and thrombocytopenic purpura have not been described.

Boric Acid.—In almost every review of dermatologic allergy there is a reference to boron poisoning from the use of boric acid either in solution or in powder form. Feeling often runs high against the use of boric acid in hospital practice. Fisher et al[72] stated that the diagnosis of boric acid toxicity must rest on demonstration of toxic concentrations in the blood or tissue of the subject rather than on the qualitative presence of this element in the urine. Sixty infants were maintained on a regimen of boric acid dusting powder for a year. The powder contained 5 per cent boric acid in talc and the amount used was 168 gm per infant per month. No significant increase in blood boron concentration was found even during periods when infants suffered minor skin irritations. The authors stated that the literature is full of striking misuse of boric acid followed by untoward results. The material was either applied in copious quantities as pure or essentially full strength powder to extensive areas of denuded or macerated skin of a small infant. Careful review of the literature does not show a single authenticated case of boric acid poisoning due to the use of borated talc. This is explained by the fact that there are significant amounts of calcium in talc which combine with the boric acid to produce a highly insoluble calcium borate that prevents absorption in toxic amounts. Boric acid toxicity is the subject of a review by Johnstone and others.[120] It is suggested that boric acid is added to talcum powder primarily as a buffering agent. The pH of unbuffered talcum powder is about 9.3; the addition of 3 to 5 per cent boric acid brings the pH to approximate neutrality. The authors saw no contraindications to the use of a boric acid

dusting powder either on the intact or damaged skin. It is emphasized that fatalities with boric acid have occurred only with inadvertent misuse of high concentrations of boric acid in powders or in solutions.

Butazolidin.—A woman fifty years of age developed aplastic anemia following treatment with Butazolidin.[182] Although she made a clinical recovery, the bone marrow response was discouraging. It is emphasized that the prognosis of aplastic anemia due to marrow pancytopenia associated with drug therapy is always grave. Spontaneous recovery may occur and it is doubtful whether there is any specific treatment that will accelerate recovery. Regular transfusion of whole blood or of packed red blood cells in order to maintain the hemoglobin level in the vicinity of 10 gm per 100 cc is the most useful therapeutic measure. Corticotropin and cortisone are probably equally effective in preventing purpuric bleeding by decreasing vascular fragility and sometimes by elevating the platelet count. In rare instances of hypoplasia of erythropoiesis, especially in children, cortisone has increased the erythroid cellularity of the bone marrow. Anemia has then become responsive to vitamin B_{12}. It is suggested that chemotherapy should be reserved for a clinical indication and not used prophylactically. The patient should have a nutritious diet and in addition 30 mcg of vitamin B_{12} every two weeks by injection as well as 1 to 5 mg of folic acid daily by mouth. Based on vague clinical impressions, the patient should also be given 1 unit of liver extract or liver solution U.S.P. daily. Mauer[153] reported a forty-eight-year-old woman who had taken 35 tablets of 100 mg of phenylbutazone (Butazolidin) over a period of twenty-two days because of a painful knee. At the end of that time an eruption appeared and her physician discontinued the drug and gave an injection of ACTH. The patient was hospitalized because of the rapid onset of an eruption, burning in the mouth with difficulty in swallowing, nausea, vomiting and a temperature of 100.4° F. Abdominal pain increased which required surgical intervention, and an acute duodenal ulcer was found. The skin eruption progressed to the point of purpura and exfoliation and became generalized. At this point the temperature, which was usually 100 to 103° F., rose to 108° F. on the twenty-sixth hospital day. Two days later the patient died. The literature suggests that phenylbutazone reactions are not related to dosage or duration of treatment. There are no known methods of predicting an unfavorable reaction. It is suggested that the drug be reserved for patients with arthropathies that are severe.

Carbromal.—Borrie[27] reported a purpuric drug eruption caused by carbromal (alpha-bromo-alpha-ethylbutyrylcarbamide) a hypnotic introduced in 1910 and popularized by Bayer under the name of "adalin." In England this preparation is available over the counter without a doctor's prescription. The usual hypnotic dose is 320 mg. Six cases are reported in detail. The purpuric eruption was remarkably constant in all with involvement of the trunk and extremities. Eruption subsided in two to three weeks after carbromal was discontinued. Increased capillary fragility was constantly present but no abnormality in the hemogram was found in any of the patients. An eruption appearing almost identical to that produced by carbromal may result from chemicals used in processing clothing which can cause capillary damage in certain individuals. This was reported by Peterkin (Peterkin, G. A. G.: Textile dermatitis in men. Arch. Dermat., 58:249, 1948). Likewise, the eruption must be

differentiated from idiopathic purpura of the nonthrombocytic type which persists from one to two months to a year and resolves spontaneously.

Chlordane.—Chlordane is a popular chlorinated hydrocarbon insecticide and pesticide that is being used extensively by farmers and home owners.[52] A number of cases of contact dermatitis have been reported among exterminators and employes of pest control firms, with little or no previous history of allergy or skin trouble. In several instances patch tests confirmed a relationship and in all instances removal from exposure to chlordane improved the skin condition. Systemic reactions with a possible allergic basis associated with chlordane exposure have been reported infrequently.

Chlorpromazine.—Denber[56] noted that chlorpromazine therapy was used in 750 patients at Manhattan State Hospital, Ward's Island, New York, New York. In fourteen psychiatric hospitals abroad, a survey of 4360 patients following chlorpromazine therapy revealed an incidence of skin eruption in twenty-five patients. Allergic skin reactions in nursing personnel have been noted in a rather alarming fashion in this country. The incidence of reactions was highest when the intramuscular route of administration was used and lowest when the drug was given orally. The author believed that the entire question of side reactions to chlorpromazine has been stressed out of all proportion to the problem of the management of psychiatric patients with a drug that has unusual potentialities in this field. Increased tendency to bleeding was noticed during treatment with chlorpromazine in 1954. Marley[148] reported a sixty-three-year-old patient who was admitted to hospital for involutional depression. She was given chlorpromazine by injection and at the end of the first week she was given 100 mg of chlorpromazine by mouth daily. Later the dose of chlorpromazine was increased to 250 mg a day and after twenty-seven days of treatment she was observed to have a spontaneous symmetrical purpura distributed on the dorsum of both feet and the front of both hands accompanied by an erythema in these areas. Platelet counts were normal. Thorough blood studies including a bone marrow study were grossly not abnormal. After eight days, at which time capillary studies were normal, chlorpromazine was again given, 25 mg twice daily, and this was cautiously increased, but after thirty-three days purpura reappeared and the drug was finally withdrawn. Hodges and Lazerte[107] reported the case of a sixty-seven-year-old white housewife who was seized with acute epigastric pain, fever and chills on September 10, 1954, and admitted to the hospital. It was learned that she had been given 25 mg of chlorpromazine twice daily orally by another physician from August 11 to September 1 for the relief of an itching dermatitis. Following studies, a provisional diagnosis of progressing obstructive jaundice was made and exploratory laparotomy was done on September 18. The immediate postoperative course was in no way unusual, but agranulocytosis developed a few days after operation and coincident with this there appeared aphthous lesions in the right tonsil fossa. On September 25, the patient died. A causal relationship between the administration of chlorpromazine, subsequent jaundice and agranulocytosis can only be assumed in this case. Granulocytopenia has been reported in only a few cases following administration of chlorpromazine and has been a mild and transient phenomenon. A case is reported by Tasker,[248] however, of a thirty-eight-year-old married woman who received chlorpromazine in a

mental hospital. About nine days after the onset of treatment, lassitude and fever developed and about three weeks after the onset of chlorpromazine, jaundice occurred and an irritating rash developed on the extremities. A diagnosis of agranulocytosis was made forty-one days after the onset of therapy and in spite of drug withdrawal and supportive measures the patient died. While transient fever, jaundice and skin eruptions are well recognized as complications of treatment with chlorpromazine, they may be taken as danger signals of a more serious blood dyscrasia if the drug is not withdrawn. Margolis and others[147] studied a group of fifty-three patients with various psychiatric disorders treated with chlorpromazine. Dermatitis of a maculopapular, erythematous, pruritic character developed in seven. The eruption involved the trunk and extremities but spared the face, mucous membranes, palms and soles. This type of sensitization should not be confused with the increased sensitivity to sunlight shown by many patients who take chlorpromazine. This sensitivity is usually confined to areas exposed to sunlight. The authors found that most of the sensitized patients could again be given chlorpromazine in small doses with gradual increase in dosage.

Cinnabar.—Lyell[140] presented a man, aged twenty-seven, before the North British Dermatological Society. The patient was tattooed thirteen years previously in red and blue without showing any local reaction at that time. Three months before presentation the red areas became acutely inflamed and painful and proceeded to slough and then heal, leaving depressed scars. Blue areas were unaffected. A multiform toxic erythema accompanied the acute stage. The red portion of a tattoo is usually done with cinnabar, a mercurial compound. The only exposure to mercury in this case was to fulminate of mercury used in detonators.

Decholin.—Coggins[43] stated that a controversy continues to rage about the importance of allergic reactions to sodium dehydrocholate (Decholin). It would seem, however, that everyone would agree that this preparation ordinarily used to determine circulation time should be employed with some caution. Its routine use, especially in patients suspected of allergy, is to be deplored.[222]

Diamox.—Agranulocytosis following Diamox therapy is reported by Pearson and others.[174] A case report is recorded of a sixty-six-year-old white woman who had been given Diamox, 250 mg daily, as an adjunct to digitalis and a low salt diet in the management of arteriosclerotic heart disease with peripheral edema. During her hospital admission she was febrile and had chills, and studies showed hematologic depression simulating that seen in patients with agranulocytic angina induced by aminopyrine, phenylbutazone, chloramphenicol, thiouracil and its derivatives, pyribenzamine, mercurial diuretics and others. This is the first report of agranulocytosis arising in the course of therapy with this medicament. The patient improved rapidly when Diamox was discontinued and she was given large doses of a penicillin-streptomycin mixture intramuscularly as a prophylactic measure against possible bacterial infection. Corticotropin (ACTH), 40 mg, was given intramuscularly daily for the first four days in an attempt to stimulate marrow recovery. A sternal marrow aspiration performed two weeks after the patient was discharged from the hospital revealed an entirely normal marrow, actively cellular, with normal platelet formation, normal erythropoiesis and granulopoiesis, and normal maturation. The previously noted maturation arrest at the metamyelocyte level was no longer present.

Fluorides.—Fluorides added to drinking water may produce allergic reactions. Patients are described in whom existing allergic manifestations flare up, especially eczema and allergic nasal disease.[259] These symptoms clear up when the patient discontinues drinking the water and eating food cooked in it; they promptly reappear upon partaking of the water again. Some develop pruritus, with or without evidence of dermatitis, from bathing in the water. There were two individuals with pruritus vulvae and pruritus ani. Major portions of fluorein are excreted through the urine, some through the bowels.

Heparin.—Massone[150] reported allergic reactions from heparin. These reactions were characterized by shock, bronchospasm and cyanosis. A case is reported of a forty-nine-year-old woman who was given 50 mg of heparin intravenously for thrombophlebitis of the left leg secondary to a gynecologic operation. A transitory feeling of warmth, hyperemia of the skin and mucosa, and a diffuse urticaria-like reaction with headache and nausea developed. The symptoms responded to epinephrine and antiallergic agents. Massone also noted symptoms of increasing sensitiveness to a regular series of heparin injections. This apparently coincides with arsphenamine hypersensitivity. The initial injections were followed by symptoms which were so mild as to be overlooked or underestimated, but they suddenly became progressively more severe during subsequent injections.

Iodides.—Pendergrass[175] and others reviewed 1371 questionnaires regarding unfavorable sequelae following the administration of contrast mediums for the study of the urinary tract. The two most commonly used mediums, iodopyracet (diodrast) and sodium iodomethamate (neo-iopax), accounted for approximately 94 per cent of the urinary tract studies. The quantity of contrast mediums injected in the average size adult was usually between 20 and 30 cc. Thirty-one deaths not previously recorded in the literature occurred after the intravenous administration of the contrast mediums. This survey covered an eleven year period (1942 through 1952) in a series of approximately 3,800,000 urograms. Sensitivity tests were performed in fifteen of the twenty-five cases of immediate death and were interpreted as being negative. Rasmussen[200] described two patients with periarteritis nodosa. Both had asthma, and iodide hypersensitivity was implicated as an etiologic factor. Possible mechanisms of iodide sensitivity were presented. The possible additional etiologic agents to be considered in periarteritis nodosa include serums, sulfonamides, penicillin, iodides, arsenicals, mercury, aspirin, dilantin, phenylbutazone, DDT, thiouracil compounds and phenobarbital. Since iodine is so extensively used, it is well to remember that it has been reported to produce asthma, angioneurotic edema and urticaria, pulmonary edema, peripheral edema, transitory pulmonary infiltrations, thrombopenic and nonthrombopenic purpura, fever, eosinophilia, arthritis, hematuria, albuminuria, localized necrotizing vascular lesions, various cutaneous lesions and lymphadenopathy. It is surprising that more hypersensitivity is not seen with the use of iodides. This would indicate that either such an occurrence is truly a rare phenomenon or it occurs more frequently and goes unrecognized. Perhaps the milder forms of hypersensitivity are unnoticed.

Iron.—British physicians have been using a new iron-dextran complex ("Inferon") which has produced nausea, vomiting, depression, fainting

and skin rash in 20 per cent of patients. Ross[213] reported two reactions which were considered to be on an allergic basis, one a delayed reaction in a man of fifty-five, and an earlier reaction after 1.5 ml was given intravenously to a youth of seventeen. Bourne[28] added another case report of a married woman, aged forty-six, who was admitted to hospital for total hysterectomy. An injection of iron-dextran complex intramuscularly was followed by angioedema, conjunctivitis and a febrile course. Although reactions to iron compounds have been rare, this new preparation seems to have a high index of sensitivity.

Mercury.—The problem of reactions to mercurial diuretics is extensively reported by Brown.[30] The important individual compounds are discussed in detail together with the mode of administration, their fate and excretion, dosage and management. Mercurialism, pain and other local reactions, gingivitis and stomatitis, gastrointestinal reactions and skin reactions, including pruritus and urticaria, are described in detail. It is important to differentiate between the various reactions discussed and to separate them from electrolyte disturbances. Mercurcial diuretics judiciously used can be given without ill effects. One clinic reported 13,000 injections of mercurial diuretics without any untoward effects. In a truly allergic patient in whom mercury sensitivity is suspected, treatment should always be initiated with a small dose of the magnitude of 0.2 to 0.5 cc. Intradermal skin tests of the mercurial diuretic and patch tests even on the abraded skin are not dependable. The intradermal injection of 0.05 cc of serum from a patient taking the mercurial in question will often result in a wheal if the recipient is sensitive to the mercurial diuretic. If a positive reaction is obtained, the patient may be able to tolerate with safety another mercurial diuretic given with precautions.

Mepacrine—Atabrine.—Paton and others[172] reported the case of a woman farm worker, aged fifty-three, who took mepacrine intermittently for discoid lupus erythematosus. Fatal aplastic anemia developed and the patient died in spite of repeated transfusions, antibiotics and steroid therapy. Custer had previously reported (Custer, R. P.: Aplastic anemia in soldiers treated with atabrine (quinacrine). Am. J. M. Sc., 212:211, 1946) fifty-seven fatal cases of aplastic anemia among servicemen in the Southwest Pacific theater where the vast majority took suppressive doses of mepacrine, 100 mg daily. In other war theaters the incidence of aplastic anemia in the services was insignificant by comparison. The reviewer notes that exfoliative dermatitis may follow the use of these compounds in psoriasis. These agents are effective in light-sensitive dermatoses, some cases of lichen planus and other dermatoses.

Para-aminosalicylic Acid.—Out of 5000 patients receiving para-aminosalicylic acid (PAS) as part of their antituberculous regimen in a hospital, fourteen developed severe allergic reactions to the drug. Cannemeyer and others[36] reported that the average daily dose of the medication was 12 gm given in three equally divided doses. Reactions occurred fifteen to forty-three days after the onset of therapy and were characterized by high temperatures, itching and various nonspecific eruptions. Lymphadenopathy was present in eleven of fourteen patients, chiefly in the cervical area. The systemic reactions were accompanied by peripheral blood findings showing a relative or absolute lymphocytosis with atypical forms and an eosinophilia. The atypical lymphocytes were similar to the cells seen in infectious hepatitis, mononucleosis, "viral" respiratory disease and allergic states. The eosinophil counts ranged from 7 to 50 per cent but

in most patients were from 12 to 25 per cent. The counts usually returned to normal within three to six weeks after the onset of allergic symptoms. Studies with heat-killed *Staphylococcus aureus* demonstrated active phagocytosis on the part of the neutrophils, eosinophils and monocytes. The lymphocytes failed to exhibit this property. Biopsies of the posterior auricular lymph nodes were made in seven patients and general hyperplasia of the nodes was found. Scratch, patch and intracutaneous and passive transfer tests produced very few significant reactions and positive patch reactions frequently followed the application of a lanolin-based ointment containing 35 per cent para-aminosalicylic acid.

Penicillin.—Hypersensitivity reactions to penicillin should be familiar to all readers of the literature on allergy. Additional reports continue to appear. Nevertheless, many surgeons, internists and general practitioners fail to recognize the importance of penicillin as a potent and dangerous agent in the production of anaphylactoid reactions. All allergists have a responsibility to the profession to keep their colleagues informed.

The literature on anaphylactoid reactions from penicillin was reviewed by Calvert and Smith.[34] A further case was reported to emphasize that moderately severe reactions can follow the use of penicillin lozenges and that there are occasional instances of severe reactions even when no history of previous administration of the drug can be elicited. The case is reported of a forty-seven-year-old, robust Army officer who went into profound shock after a penicillin injection. He responded to 3 ml of nikethamide intramuscularly as no accessible veins were available for more direct administration.

Allergy to penicillin in four patients was reported by Peters and others.[177] One patient died after an intramuscular injection and in three patients episodes of unconsciousness and shock developed following the use of penicillin troches or tablets. The death occurred in a sixty-nine-year-old asthmatic woman who was given an injection of 600,000 units of procaine penicillin intramuscularly following a nasal operation. She died within twenty minutes after the injection, despite emergency treatment. An autopsy failed to demonstrate the cause of death. This report stresses the fact that shock-like reactions may develop from the oral administration of penicillin. Campbell[35] reported the death of a woman, aged forty-two, with a history of chronic bronchitis who had previously been given penicillin, in 1949, with no ill effect. It was determined that she was in labor and, because of a fever of 101° F., she was given 400,000 units of penicillin intramuscularly. One hour later she vomited and this was followed by unconsciousness and stertorous breathing. The nurse administered oxygen and sent for medical aid. The patient was found to be dead. A postmortem examination showed nothing unusual and the pathologist decided that death was due to anaphylaxis caused by the penicillin injection to which she had previously been sensitized. This case is of interest because of the fatal termination which was delayed as long as one hour after an injection of penicillin.

Morrisset[160] reported the case of a thirty-nine-year-old man who was given an injection of 400,000 units of procaine penicillin when he complained of a sore throat and rhinorrhea. There was no history of allergy. The patient had received about twelve injections of procaine penicillin, the last having been given thirty days previously. Approximately one minute after the penicillin had been injected, the patient complained of tingling all over, vomited twice, stated he "couldn't breathe," and

collapsed. The blood pressure and pulse could not be obtained. Respiration was gasping, a few high pitched rales could be heard but there were no normal breath sounds. The patient became incontinent. Epinephrine, 1 cc of a 1:1000 solution, was given intramuscularly. Cortisone, 100 mg, and isotonic sodium chloride solution, 300 cc, were given intravenously, and oxygen administration was started. Intermittent injections of epinephrine were required in doses of 0.5 to 1.5 cc intravenously at periods of three to five minutes. One hour later the patient was still cyanotic; the blood pressure reading was 60 mm Hg systolic and 30 mm Hg diastolic, but he had regained consciousness enough to state that he felt better. It was thought that the recovery was due to the prompt use of epinephrine and cortisone intravenously. Oxygen did not seem to be of use until obstruction was relieved at the level of the bronchioles. Wright[267] reported the case of a woman, aged forty-two, who had been given six intramuscular injections of penicillin daily in October, 1954. On February 2, 1955, she was given 300,000 units intramuscularly because of recurrent bronchitis and pyrexia. Within ten minutes a reaction occurred consisting of cyanosis, severe dyspnea and shock. The patient responded to symptomatic treatment, including epinephrine, 1:1000, and made a complete recovery. Cruz Hernandez[54] reviewed the literature of anaphylactoid shock due to penicillin and reported a case with an acute course and recovery following administration of penicillin. The patient was given epinephrine, oxygen, antihistaminics and supportive fluids intravenously. Dumm and others[61] reported the case of a twenty-one-year-old man with a background of allergic rhinitis and sinusitis who was given an injection of a mixture of penicillin-streptomycin procaine. Within a few minutes a shock reaction developed, characterized by dyspnea, cyanosis and vomiting. The pulse became imperceptible. Following the intravenous use of ACTH and a transfusion of 1500 ml of blood the patient recovered. Skin tests were negative to both penicillin and procaine. A marked immediate reaction, however, was obtained with 1:10,000 dilution of dihydrostreptomycin. The patient admitted the topical use of streptomycin previously. A fifty-three-year-old woman was given one tablet of oral penicillin, 200,000 units, for a sore throat.[125] Within a minute or two she noted numbness and tingling of the lips, followed by swelling and loss of consciousness. After admission to the hospital, the patient was given Levophed (levarterenol), 4 mg per liter of physiologic saline solution, with cortisone, 125 mg intramuscularly. For the first nine hours it was necessary to give levarterenol continuously to maintain the blood pressure at near normal levels. Her condition gradually improved and she was discharged three days after admission in good health. She had received penicillin by intramuscular injection on numerous occasions and had previously taken penicillin by mouth, with no ill effect. She had a history of respiratory symptoms following exposure to dust. In a review of dermatologic therapy, Downing[59] mentioned that a hypoallergic penicillin "O," "compenamine" and "BT" may be useful in certain patients with reactions or known to be hypersensitive to either soluble penicillin G or procaine penicillin, but may also cause reactions. The local and systemic complications of antibiotic therapy were outlined by Weinstein.[261] Various toxic eruptions including morbilliform, scarlatiniform, urticarial, vesicular, bullous and purpuric eruptions may occur, and some may progress to exfoliative dermatitis. Purpura may be present with or without thrombocytopenia. "Drug fever" may be the only manifestation of sensitization to an anti-

biotic or may precede or accompany other reactions. The disappearance of fever is directly proportional to the speed with which the causative drug is excreted. The most serious allergic complications follow the use of penicillin and streptomycin, and the anaphylactic deaths that have occurred are emphasized.

Allergic hypersensitivity to penicillin has been shown[142] in 12.17 per cent of 156 workers in a penicillin factory who came in contact with the finished product. Scratch tests with powdered penicillin diluted in one drop of isotonic sodium chloride solution were positive, as were the intracutaneous tests with 0.05 cc of penicillin solution containing 2000 units of the antibiotic per cubic centimeter. Patch tests were also done with penicillin solution containing 10,000 units per cubic centimeter. It was found that the intracutaneous test was the most valuable of the three. Asthma was found in three workers, allergic dermatitis in fourteen and angioedema in two. A program was established among these workers to protect them from subsequent exposure to penicillin, including injections which might lead to anaphylactic shock. There are a number of reports in the literature which state that sensitization to penicillin in children is uncommon. Matheson and Elegant[151] reported that 390 of a group of 391 children who had received penicillin injections on many occasions did not demonstrate skin sensitivity to this antigen. Another group of six children who had experienced severe constitutional reactions following administration of penicillin was tested and it was found that four of five children who had immediate or accelerated reactions and one child who had severe delayed constitutional symptoms had immediate positive skin tests to penicillin. Two of three such cases had positive passive transfer skin tests. Most of the constitutional reactions to penicillin occurred in children with an atopic background. One child suffered constitutional symptoms following a scratch test with penicillin containing 5000 units of penicillin per milliliter. A negative skin test with penicillin does not rule out potential anaphylactic-like reactions. There was no dermal sensitization to procaine in the entire series of patients tested. A survey of the recent literature on fatal and near fatal anaphylactic reactions to penicillin was made by Lapin.[126] Reactions to intramuscular injections of penicillin have been increasing in frequency in adults but are still rare in pediatric practice. No fatal or near fatal anaphylactic reactions have been reported due to oral administration of penicillin in children. The author described his experiences in the oral administration of penicillin to children for routine prophylaxis of upper respiratory infections. The original work appeared in 1948. Four hundred thousand units of penicillin G potassium tablets was given at the first dose and then 200,000 units every four hours. The soluble type was prescribed for infants and children under three years of age and the buffered type for those over three years. The dose was mixed with milk or other foods and no effort was made to give the medication when the stomach was empty. This dosage routine should result in a satisfactory concentration of penicillin over most of the twenty-four hour period. Four hundred and two children from three months to ten years of age seen in private practice were used in this study; 0.5 per cent sustained a mild urticarial reaction. There were no major reactions. It is suggested that oral penicillin be used routinely in an effort to avoid the complications of upper respiratory infections in infants and children.

There are no known reactions to Duponal following its inhalation in mists.[196] Triton is the main ingredient of Alevaire and has a pH of about 10; inhalation of this material may produce very severe irritation of the bronchial tree. Alevaire when used in small quantities has very little clinical effect and produces no untoward reactions. If a striking effect is to be produced, it has been suggested that about 50 ml should be inhaled. Reactions to mixtures of antibiotics and wetting agents may be due to inhalation of the antibacterial drugs. Asthma, anaphylactoid reactions, skin eruptions of various types and superinfections of the lung have been described following repeated inhalation of penicillin or streptomycin. It has been suggested that the individuals who develop severe reactions to hypersensitivity to antibiotic agents are those who have an allergic background, especially a history of atopic allergy. Patients who have Schönlein-Henoch purpura may be allergic to any one of a number of factors. The allergen may be a bacterium or a bacterial product. In this case, the disease is often preceded by a hemolytic streptococcus infection of the upper respiratory tract and the antistreptolycin titer is increased. Jensen[117] studied the disease in a number of patients and found two patients who were allergic to fish, shrimp and carp. In a third patient, this form of purpura developed after three injections of penicillin. In reviewing his material, Jensen reported involvement of the extensor surfaces of the extremities, flexor folds of the elbows, the wrists and gluteal and perigenital regions. The trunk and face are usually not involved. Fairly well-defined urticarial lesions may appear at the onset. These become papular and then take on the characteristic appearance. Petechiae may occur but ecchymoses are rare. Abdominal symptoms also occur in some patients. Joint symptoms are well known in this disorder. The most dangerous complication is renal involvement.

Siegal[233] studied sixteen allergic individuals with known inhalant and food sensitivities. Intracutaneous tests with polio vaccine yielded a negative or ± reaction in fourteen of the individuals, and in two of the tested subjects, a 1+ reaction was obtained. Intracutaneous tests were performed on known penicillin sensitive subjects. Negative results were obtained to the vaccine in contrast to a strongly positive reaction obtained on one subject with a 10 unit per milliliter dilution of penicillin. The subcutaneous injection of 1.0 ml of the vaccine failed to induce either a local or systemic reaction on a penicillin hypersensitive patient. It is thought that the Salk vaccine probably contains less than 0.5 unit of penicillin per milliliter. Allergic patients whose sensitivity consists of reactions to animal danders and proteins can probably tolerate Salk vaccine without any difficulty. The question is raised whether children receiving Salk vaccine will not be sensitive to the use of penicillin and streptomycin.[193] While it is difficult to answer such a question in absolute terms, it has been shown that tests for dermal reactivity of about 150 children who had been vaccinated seven months earlier showed no indication of the development of sensitivity as demonstrated by skin tests. The thousands of children who have already been vaccinated show no indication of the development of sensitivity to penicillin and streptomycin as indicated by the appearance of untoward reactions to the vaccine. A communication[88] from the Food and Drug Administration reported that a survey on market milk showed that out of 474 samples, 11.6 per cent contained penicillin, the minimal amount detected being 0.003 unit and

the maximal 0.08 unit per milliliter. It was the opinion that the above amounts of antibiotics could provoke a reaction in a highly sensitive individual. It is probably not commonly known that penicillin may contaminate syringes and that some of the antigenic principles in penicillin remain active despite boiling for many hours. Patients who have developed severe reactions to the alleged "first" administration of this antibiotic may have been sensitized previously by contaminated syringes. Moreover, patients who have received innocuous substances and then suffered severe reactions may have been sensitized previously and the subsequent reaction was elicited by this contamination problem. Coleman and Siegal[46] reported a case of a twenty-nine-year-old Negro nurse in whom penicillin as a syringe contaminant induced a severe immediate allergic reaction. A solution of penicillin G was boiled for sixteen hours, and its antigenic activity was still pronounced and could be readily demonstrated by passive transfer tests. It is suggested that the syringes used for penicillin be so designated and care should be taken in avoiding contamination of sterilizers and other syringes with penicillin. Another solution to the problem might be the use of disposable cartridges in connection with penicillin administration.

Berger and Eisen[21] tested 1000 patients with procaine penicillin using scratch, intradermal and patch tests. This large group of patients included allergic and nonallergic individuals and persons definitely known to be penicillin sensitive. Of the 1000 patients given penicillin, twenty-four had positive reactions. In the twenty-four positive reactors there was absolutely no relation to the three groups tested. It was thought that combining penicillin with an antihistamine may diminish or abort the delayed manifestations but this measure would not prevent an anaphylactic reaction. The authors believe that skin tests cannot be depended upon to determine penicillin sensitivity. In a discussion of the paper by Berger and Eisen, Coleman[45] stated that he believed that the authors came to the wrong conclusion. They stated that skin testing for penicillin sensitivity is unreliable and should be discarded and yet one patient reported promptly developed anaphylactic shock after skin testing with 20 units of procaine penicillin. If this patient had not been tested, but rather given a therapeutic dose of penicillin which could be at least 15,000 times greater than the test dose used, a fatal outcome would most likely have resulted. It is suggested that skin testing to penicillin be done because patients with reagins to penicillin will develop a severe, immediate, allergic shock or anaphylactic reaction following full doses of the antibiotic. In spite of the extensive literature on penicillin allergy, Tuft and others[254] found that there is no standard method of skin testing for penicillin allergy. They studied 629 patients, including 134 who had never received penicillin previously, 463 who had been given penicillin with no known allergic reaction and thirty-two who had experienced an allergic reaction following the administration of the drug. Of 495 patients who had received penicillin, specific positive reactions to tests occurred in 1.8 per cent. The incidence of positive reactions, however, was higher in patients with a history of allergic reactions to penicillin, 9.4 per cent, than in those without such a history (1.3 per cent). Most positive reactions were graded a 1+ response even with high concentrations of penicillin solutions. It is emphasized that a positive reaction to penicillin may be highly evanescent and disappear within a short time. Two or three months

after a positive reaction, a patient may have negative skin tests and still be highly allergic. Results of a negative test, therefore, do not exclude the possibility of a subsequent positive reaction, especially if the patient has an allergic background and has previously received penicillin. The preferred dilution of penicillin is 10,000 units per cubic centimeter and the amount suggested for an intracutaneous injection is 0.02 cc. A scratch test is advisable before the intradermal test. Siegal[232] noted the shortcomings of skin testing in penicillin sensitivity and stated that the association of a strongly positive immediate skin test read at fifteen minutes with penicillin anaphyaxis has been documented by many authors. Siegal and co-workers reported positive passive transfer in every one of ten instances of anaphylactic shock with a high titer of reagins in several, indicative of the presence of a positive immediate direct test. Nevertheless, false negative tests have been known to occur. It is only the positive, not the negative, test that is of clinical value. Siegal believed that the occasional individual recovers tolerance for penicillin even after a reaction of some type has occurred.

A number of investigators have attempted to reduce anaphylactoid reactions to penicillin by the simultaneous administration of antihistamines orally or parenterally, or both.[6] Some reports suggest that a reduction in the incidence of untoward reactions is thus obtained, but the ideal results of no reactions will never be reached. Mathews et al,[152] in a controlled study with more than 2,000 injections of penicillin given to university students at Michigan, found no significant differences in the incidence of severe or delayed penicillin reactions between the controls and those receiving antihistamines by the oral or parenteral route. On the evidence at present, the simultaneous administration of any antihistamine cannot be recommended as a worthwhile routine precaution. It has been well known that the combination of an antigen and an antihistamine may prevent severe reactions. Frankel and Stutsman[79] studied 512 ambulatory men at the Marine Corps air station in Miami, Florida. A total of 1,157 injections of penicillin combined with chlorprophenpyridamine maleate (Chlor-Trimeton®) was given during a four month period. In patients who had a negative history of either penicillin injections or reactions to penicillin, the subsequent penicillin injections were combined with 20 mg of Chlor-Trimeton. There were fifteen known reactors to penicillin and these patients were subsequently given Chlor-Trimeton, 40 mg, mixed with 600,000 units of penicillin. It is reported that not one of the fifteen known reactors had any kind of reaction to penicillin administered in combination with Chlor-Trimeton maleate. None of the 540 injections of penicillin with Chlor-Trimeton in nonreactors was followed by any kind of reaction either local or general. No side effects attributable to the antihistamine were observed. In a control group of men who received 583 injections of penicillin alone, three had angioedema and serum sickness.

It has been known that many nurses have had to abandon their career on account of sensitivity to penicillin. O'Driscoll[167] found it possible to desensitize a nurse who otherwise would have given up her profession because of reactions to this agent. Previous failures reported in the literature were the result possibly of inadequate dosage. Details of the technique are recorded. The patient was given a series of twenty-seven injections of progressively increasing doses of penicillin, usually at daily intervals, accompanied by antihistaminic drugs. Binns[23] reported

successful desensitization of a penicillin-allergic individual with thirteen injections of penicillin plus an antihistamine. In four additional patients, desensitization was strikingly successful in two; two others had indifferent responses. A fifth patient lost his eczematous reaction early in the course of penicillin desensitization, but later urticaria developed despite the simultaneous injection of antihistamine. This patient was able to tolerate penicillin applied locally in spite of these side reactions. He had been known to be sensitive to the local application of penicillin for four years. There is undoubtedly considerable variation between individuals in their ability to be "desensitized" to penicillin.

A sixty-four-year-old white man was treated with penicillin-streptomycin on admission to a hospital because of pneumonia and congestive heart failure. He was readmitted later with drug sickness manifested by urticaria, multiple arthralgias and fever. Peripheral blood was found to contain "L.E." cells. The patient was treated with ACTH and recovered. Subsequently, no "L.E." cells were found in follow-up care. It is believed by Paull[173] that the "L.E." phenomenon appeared in this patient as a result of a severe penicillin reaction. The reviewer notes that this is the second therapeutic agent which may result in the production of the "L.E." phenomenon. A number of reports of this reaction to Apresoline was recorded in the 1955 review of Dermatologic Allergy.[82]

Pentothal.—Reactions to intravenous pentothal in a patient included delirium. The patient was semicomatose for several hours following surgery, according to Service.[226] The reviewer notes that many patients have this difficulty with pentothal. It may not be on an allergic basis. Pentothal does not relieve pain; its function is to produce unconsciousness. Nitrous oxide is the effective pain reliever.

Piperazine Citrate.—Ratner and Flynn[201] made experimental studies with piperazine citrate (Antepar) and found that they could not sensitize the guinea pig using standard experiments and criteria of sensitization with drugs set up by Chase. An evaluation of the drug was made because cases of what appeared to be allergic dermal reactions from the use of Antepar were reported to them. In an analysis of twenty-seven such cases, eight had insufficient data, eleven manifested symptoms which appeared to be unrelated to the drug, and eight appeared to have had a serum sickness-like reaction. The authors concluded that insofar as no authenticated case of allergy to syrup of piperazine citrate (Antepar) has been presented heretofore in the literature and since this drug has been shown to be nonanaphylactogenic in a lower animal, it should be regarded as a nonallergenic drug. The reviewer notes that in the paper by Mayer, Eisman and Jaconia[156] it is stated that "efforts to produce in guinea pigs such allergic side effects as Nirvanol-disease or the usual anaphylactic reactions with penicillin have been fruitless." Penicillin anaphylaxis in man, however, is a dramatic and frightening entity. In a further personal communication, Ratner states, "My experience with animal experimentation has clearly demonstrated to me that if a substance thoroughly tested on the guinea pig does not show antigenic properties, it usually is a definitely weak antigen. All strong antigens do show sensitivity in the guinea pig."

Procaine.—It is common dental practice to use epinephrine in dilutions of 1:50,000 to 1:100,000 combined with procaine for routine dental work.[203] Occasionally reactions occur and these may be attributed to

the epinephrine or to the stress produced by the dental procedures. Use of epinephrine with procaine for dental surgery presents no special hazards in persons with heart disease if no more than 10 cc of epinephrine, 1:50,000, is used and no more than 0.2 mg of epinephrine in any form at one procedure.

Salicylates.—A case is reported[158] of a bus driver, aged fifty-two, found to be suffering from mild rheumatic fever. He was given sodium salicylate, 20 grains, with sodium bicarbonate, 30 grains, to be taken every four hours. After ten days of this therapy the patient was found to be delirious and have a rash and he was hospitalized. Shortly after admission the patient suddenly collapsed and died. The findings at postmortem examination were those of acute cerebral and pulmonary edema.

Streptomycin.—It is stated that sensitization to streptomycin acquired by handling the drug[9] does not disappear spontaneously while contact with the drug is maintained. The simplest technique for determining sensitivity to streptomycin is to inject 25 to 100 μg. in 0.1 ml intradermally. If the patient is sensitive, erythema appears which may be observed at six, twelve or twenty-four hours after the injection. The test should not be regarded as negative unless the full dose of 100 μg. has been given in the relatively nonsensitive patient. Desensitization is feasible although a little tedious. Hansen and Cleve[100] reported the case of a twenty-two-year-old Negro with pulmonary tuberculosis who received para-aminosalicylic acid in doses of 3 gm four times daily for approximately two weeks and 1 gm of streptomycin intramuscularly every third day for the same period. There was no personal or family history of allergy. At the end of two weeks a high fever and a pruritic morbilliform eruption developed which covered the entire body. Streptomycin was discontinued but, in spite of this, severe conjunctivitis, lymphadenopathy, anorexia, a hacking cough and a fever of 105° F. developed. Blood studies were made and showed an absence of eosinophilia. There were, however, numerous granular and hyalin casts in the urine sample. When all symptoms had subsided, treatment with para-aminosalicylic acid was again started and subsequently the patient was given 1 gm of dihydrostreptomycin intramuscularly. Three hours later he noted severe pruritus of the genitalia, and studies showed a 23 per cent eosinophilia. The patient suffered a convulsive seizure and died. A case report is presented by Esteves and Brandão[67] of a woman, twenty-three years of age, with a family history of eczema, colitis, migraine and asthma. Because of roentgenologic findings she was given Isoniazid and para-aminosalicylic acid, as well as streptomycin by injection. Shortly after this, she became febrile and a localized eczema developed, followd by Löffler's syndrome and erythroderma with total loss of hair. Reactions to patch tests were positive to streptomycin, which is rare following intramuscular administration. Reactions to para-aminosalicylic acid on patch tests are rather common and positive patch tests to Isoniazid are extremely rare. This drug eruption may have been of the allergic eczematous contact type and engendered by an injection, in which case the patch test reactions would be positive. Jahrmarker[114] reported the successful desensitization of two nurses who had become allergic to streptomycin. Urticaria was the presenting symptom. Desensitization was carried out with subthreshold doses in the beginning by the subcutaneous route two to three times weekly. One patient was successfully desensitized. The second patient did not tolerate treatment very well. It was important in both of these patients to give

them tolerance for therapeutic doses which would have been advantageous in the event of an intercurrent tuberculosis. It is believed that clinical success seems to depend not so much on the size of the doses used for desensitization as on the degree of sensitivity that existed before treatment. A thirty-nine-year-old woman treated for pulmonary tuberculosis with streptomycin and para-aminosalicylic acid developed agranulocytosis. The chief feature of this clinical report by Mahrer and Maret[143] lies in the importance of watching the patient on readministration of certain drugs. The patient had been given streptomycin and Isoniazid, which were discontinued because acid-fast bacilli were not seen in an excised granuloma. Six weeks after operation, *Mycobacterium tuberculosis* was reported on culture and the patient was given para-aminosalicylic acid and streptomycin. This was followed by agranulocytosis. Sensitivity to para-aminosalicylic acid was also suspected, but it is of interest that in this case report the blood changes parallel those of the thiouracil group of drugs. Most reactions occurred when the drug was discontinued and then readministered after an interval of from one to three months. This patient recovered with the use of ACTH and cortisone.

Sulfones.—From time to time patients are seen with periarticular swellings which cannot be explained by association or lack of association with the various arthritides. Spring[238] reported joint swellings following the administration of sulfathiazole for chancroid. Another patient complained of similar symptoms after administration of penicillin and in one case the only drug incriminated was thyroid. These swellings resemble the findings in intermittent hydroarthrosis and recurrences may frequently be attributed to certain food excitants. Precautionary measures to eliminate the frequency and severity of allergic or possible allergic reactions to drugs were outlined by Lowell.[138] The incidental and unnecessary exposure of patients to sulfonamides and antibiotic drugs should be held to a minimum. The drugs which are known to be effective and relatively safe when given by injection should preferably not be administered topically as ointments or nose drops. Other antibacterial agents should be used in this fashion. Accurate bacteriologic diagnosis and sensitivity studies are helpful in the proper management of patients requiring agents to combat infection. It is suggested that multiplicity of drugs used simultaneously should be held to a minimum. Furthermore, potentially hazardous drugs should be given in an extremity rather than the buttock to allow for the adequate application of a tourniquet. This applies particularly to patients who have received penicillin. Care must be taken not to enter a vein when giving subcutaneous or intramuscular injections. Whenever it is feasible, sulfonamides, penicillin and other antibiotic drugs should be given orally since the incidence of allergic reactivity by this route is much less.

Two patients who were suffering from a generalized erythroderma thought to be due to arsenicals were treated with Cibazol by Groenewegen.[95] In one patient, five days of BAL treatment was ineffective. Cibazol, a sulfonamide preparation, was given in doses of 3 gm per day for seven days and this was followed by decreasing temperature and dramatic improvement of skin lesions. Other reports suggest that erythrodermas caused by drugs do not require more than ten days of Cibazol treatment for complete healing. As a rule BAL therapy must be continued for an average of about twenty-one days in the more serious cases

to effect adequate control. The mode of action of sulfonamide therapy in exfoliative erythroderma is not understood. Gaul[87] studied the minimal dose required to reproduce a drug eruption in a sensitized patient. A patient sensitive to sulfa drugs was given sulfamerazine in a dose of 0.25 gm. This was followed by a severe generalized flare-up and the same experience occurred with two other sulfa preparations. In order to determine the minimal dose that would produce a flare-up in this patient, dilutions were made of sulfadiazine powder as great as 1:10,000,000. The patient was instructed to take a single capsule every other day. It was found that flare-up occurred with a strength of sulfa of 1:1,000. Gaul found that the appearance of a macular erythema was the first sign of a positive reaction to a minimal test dose. Itching was noticed after the development of the erythema. The reaction time was between six and eight hours. The severity of the test reaction was dependent on the size of the dose administered. This information should be helpful for those who wish to determine the existence of sensitivity in a patient before a drug is to be administered. Fox[74] presented the case of a married woman of thirty-three who developed a butterfly eruption and fever following the use of sulfadimidine tablets. Because of the persistence of the eruption and the fever, it was necessary to rule out sulfonamide sensitivity rash; lupus erythematosus and bullous erythema multiforme. The condition ultimately subsided when the drug was discontinued, but the patient reported annoying hair loss. Falling hair is common after sulfonamide sensitivity but the ultimate prognosis is good. Marked residual pigmentation at the site of the lesions often persists for three months after the onset of the illness. In reference to sulfonamide therapy, the incidence of agranulocytosis is difficult to determine. It is probably of the order of 1 in 1,000 to 1 in 10,000 of cases treated. Sulfadimidine and sulfadiazine are probably safer in this respect than sulfathiazole and sulfapyridine. Most of the reported cases have occurred after heavy dosage for a week or more or after the prolonged use of small doses as in the prophylaxis of acute rheumatism.[8] As a crude guide, it may be said that the total dose should not exceed 50 gm nor the period of administration twenty-one days. The reviewer recently saw a patient in whom severe methemoglobinemia developed following the use of diason (sulfone) for generalized herpes gestationis. It is to be remembered that the new oral agents for the treatment of some forms of diabetes are either sulfones or their analogues.

Tetracycline.—Welsh[262] reported a crossed fixed drug eruption from three antibiotics. A case history is presented of a patient who was given tetracycline in December, 1953. An upper respiratory infection appeared in May, 1954, and the drug was again administered. In June, 1954, one dose of tetracycline, 250 mg, was administered orally. Within an hour violent pruritus occurred at all sites of the former eruption which had appeared after chlortetracycline was given and which was accentuated after administration of oxytetracycline. The sites of flare were easily identified by the residual pigmentation still present. Erythema, urticaria and bullae developed and pruritus became generalized. Symptoms subsided in two days and objective evidence of the lesions disappeared in five days. Pigmentation at each site of the fixed eruption, which had become more pronounced after use of the oxytetracycline, was still more pronounced after tetracycline was administered. The author concluded

that the crossed fixed drug eruption was due to the tetracycline ring common to all three antibiotics. Beckett and Foxell[19] reported the case of a man, aged seventy-seven, who developed thromboyctopenic purpura associated with oxytetracycline therapy for pneumonia. Sulfonamides and chloramphenicol were also used in the course of his illness which proved to be fatal, but the sulfonamides were used for only twenty-four hours in a total of 2.5 gm and the bleeding did not begin until three weeks later. Chloramphenicol had been applied to the ear only on three occasions within eighteen hours and it was very doubtful that this would have a toxic effect on the marrow. Only three cases of thrombocytopenic purpura have been found due to mercurial diuretics which were used in this case. There was almost complete absence of any member of the megakaryocyte series suggesting that the action of oxytetracycline was to produce directly or indirectly a selective marrow depression affecting only the precursors of the platelets.

Tar.—A case history of a three-month-old baby boy with an extensive and severe eczema is described. The patient was treated with an ointment containing 2.5 per cent crude coal tar and 5 per cent benzocaine in a water-soluble base to about half of the body, and 1 per cent hydrocortisone in Eucerine to the other half. Goluboff and MacFadyen[92] reported further that oxytetracycline and phenobarbital were given internally. On the day after admission a moderate diarrhea developed and kaopectate and neomycin were prescribed. In the meantime the skin responded rapidly and equally well on both sides of the body. The infant suddenly became critically ill on the fifth day with manifestations of cyanosis, anoxemia and symptoms suggesting collapse. Methylene blue, 1.5 to 2 cc. of a 1 per cent solution intravenously, resulted in a rapid remission. Laboratory evidence of methemoglobinemia was obtained. There was no accounting for this unusual symptom from any agent except the benzocaine and crude coal tar. Although toxic effects from the absorption of phenolic compounds in tar, resorcin and phenol topically applied are well known, the finding of methemoglobinemia is unusual.

Nitrites.—Trinitrin ($C_3H_5[O.NO_2]_3$), a vasodilator drug, caused thrombocytopenic purpura in a man aged sixty-five suffering from coronary heart disease.[230] Erythrol tetranitrate ($C_4H_6[NO_3]_4$) could be administered without reaction. Skin biopsy showed swollen endothelium and much blood was disintegrated outside the capillaries. Bleeding time was normal and there was no bleeding from mucous membranes and viscera other than the skin. Readministration of trinitrin was followed by prompt reduction in platelets within an hour. This case showed the same histologic features as a case of thrombocytopenic purpura previously reported by Highstein and Zeligman (Highstein, B. and Zeligman, I.: Nonthrombocytopenic purpura caused by mentholated cigarettes. J.A.M.A., 146:816, 1951).

Vaccines.—Strauch[244] quoted a case by Kile who noted erythema multiforme reaction following use of Salk vaccine. It is known that the vaccine contains a small amount of penicillin and merthiolate in addition to the virus, and the toxic erythema could be due to either of these agents.

Vitamins.—It is said that the ratio of serious reactions following the intravenous injection of vitamin B complex is exceedingly small when compared to the number of injections given. Reactions to thiamine, how-

ever, have been observed almost from the time of its first isolation, and in the past fifteen years the records of 203 cases, two of them fatal, have been documented. Some reports suggest that the mechanism of death is on an anaphylactic basis and others negate this mechanism. Nicotinic acid or its derivatives may also produce toxic effects on parenteral administration. Reports of death have not been recorded and it is advised[192] that wherever possible these agents should be given orally. In most instances deficiencies of vitamins can be adequately met by oral administration.

CORTICOTROPINS AND STEROID HORMONES

A number of experiments to demonstrate absorption of hydrocortisone applied locally have previously been reported. Malkinson and Ferguson[144] demonstrated absorption in patients using radioactive C 14 to indicate epidermal penetration. There has been some evidence that adrenalectomized animals may be kept alive by inunction with various steroid preparations. Witten and others[264] used a colorimetric test, detecting the presence of 17, 21-dihydroxy-20-ketosteroids including hydrocortisone and some of its metabolic derivatives in blood and urine samples. They found that in thirteen of fifteen subjects there was no notable difference in the levels of blood or urine samples before and after inunction. The oral administration of steroids, however, regularly increased the urinary level of 17,21-dihydroxy-20-ketosteroids. Their finding suggests that there is no danger of systemic effects from the topical application of hydrocortisone even for long periods. Their subjects were patients with generalized skin diseases. Six normal male volunteers were also used. Allison and others[2] studied the effect of heat applied to the ear chamber of the rabbit by means of a platinum wire. Intensive inflammatory changes which follow may be prevented by injections of 25 mg of cortisone twice daily for three days before the experiment is repeated. Vasoconstriction is prolonged and vasodilatation is delayed and decreased. Arterial tone after injury is maintained and this suppresses edema and perivascular accumulation of erythrocytes. Significant endothelial sticking is delayed and never reaches the intensity seen without the drug. Leukocytic thrombi are noted only occasionally after use of the drug. The anti-inflammatory effect of cortisone apparently is not due only to vasoconstrictive properties. Protection of endothelial cells and leukocytes from tissue products that initiate inflammation is also noted.

Because of the need of emergency utilization of steroid hormones (anaphylactoid reactions), it has always been of interest to see how rapidly the various preparations are absorbed. When hydrocortisone is given orally, there is a rise in the plasma 17-hydroxycorticoids with a peak in about one hour and a return to control level in four to eight hours. When hydrocortisone was given intravenously at the rate of 12 mg per hour for eight hours, eosinopenia and a rise in urinary potassium were noted in one hour. Intravenous hydrocortisone has a demonstrable effect on the eosinophils in one hour and a major effect in three hours with a residual effect for twenty-four hours. The effect of cortisone given orally was about the same as that of hydrocortisone given orally but less effective, as would be expected. The intramuscular route was inefficient and slower. Grater[94] determined the speed of action of intravenous hydrocortisone by utilizing the vital capacity, maximal breathing

capacity and total eosinophil count of asthmatic patients. From 100 to 300 mg of hydrocortisone was infused over a six-hour period. One patient who had severe urticaria with laryngeal edema was given 200 mg of hydrocortisone intravenously over a fourteen hour period. One hour after the onset of the infusion there was subjective improvement of the itching and the wheals had decreased in diameter. In five hours the urticaria had disappeared completely. Burrage and others[32] favored the use of intravenous hydrocortisone in severe cases of asthma requiring hospitalization. In adults, an intravenous drip of 1,500 ml of 5 per cent glucose containing 300 mg of hydrocortisone is used. Eight-hour flow is suggested, followed by oral administration of 50 mg of cortisone or hydrocortisone every six hours until the patient is asymptomatic. In infants and children an intravenous drip of 100 ml per kilogram of body weight of 5 per cent glucose containing 3 to 5 mg of compound F per kilogram of body weight is given over twenty-four hours. Then 3 to 5 mg of cortisone or hydrocortisone per kilogram of weight is given orally in divided doses every twenty-four hours until recovery. In atopic dermatitis, 2.5 per cent hydrocortisone ointment, as well as 9-alpha-fluorohydrocortisone ointment 0.1 per cent and 0.2 per cent, often suppresses symptoms to such a degree that the skin improves or clears. At least three applications in twenty-four hours should be planned. Recurrence may follow when therapy is stopped. Local therapy has no side effects. Systemic cortisone or hydrocortisone may be used and dosage schedules follow those described under asthma for both children and adults. Children with eczema have been maintained on daily administration of cortisone orally for many months without many severe side effects. In severe cases of generalized contact dermatitis a short course of compound E or F may be indicated. In treating drug reactions it is important to remember that when the response is anaphylactoid in type, corticosteroids would be of no value because either death or recovery would occur before they could be effective. It is stated that corticosteroids have little or no place in the therapy of urticaria and angioneurotic edema. Patients are rarely encountered with frequent attacks of laryngeal swelling of such magniture that life is threatened. Recurrent laryngeal edema requiring frequent emergency tracheotomy in one patient was successfully treated by three short courses of cortisone.

In an extensive review, Russell and others[218] reported excellent results with hydrocortisone ointment in most patients with anogenital pruritus, lichen simplex, infantile eczema, discoid eczema, chronic idiopathic eczematous dermatitis of the hands, otitis externa and pruritic psoriasis of the anogenital area. In the latter condition, however, the results depended on the vehicle rather than on the hydrocortisone.

Three hundred patients treated with hydrocortisone acetate and hydrocortisone-free alcohol were investigated by Mullins and Shapiro.[161] Marked improvement was obtained in 177 patients, moderate in seventy-eight, slight in thirty-four and no improvement in eleven patients. Thin-skinned areas, such as the eyelids, periauricular and the anogenital regions, responded better. Response was most satisfactory in contact, eczematous and atopic dermatitis. Seborrheic dermatitis, psoriasis and lichen planus present on thin-skinned areas gave a satisfactory response. The authors were particularly impressed with the initial response of the patients with cutaneous infection with *Candida albicans*. Church[40] reported a series

of 105 cases of eczema and dermatitis treated with 1 and 2.5 per cent hydrocortisone ointment. Eroded and exuding eczema and dermatitis healed rapidly, while lichenified eczema showed little improvement. Good results were obtained in acute contact dermatitis, nummular eczema, atopic eczema and perianal dermatitis. Lichen simplex, lichenified atopic eczema, and lichenified cases of anogenital pruritus responded poorly. The addition of oxytetracycline to 1 per cent hydrocortisone ointment was found to have a favorable effect in cases of secondarily infected dermatoses, according to Stritzler and Frank.[245] Examples of conditions treated were impetigo, atopic eczema with secondary infection, stasis ulcer with secondary infection, retroauricular dermatitis, nummular eczema, housewives' eczema, perifolliculitis (Bockhart's impetigo), external otitis, ecthyma, sycosis vulgaris, and stasis dermatitis with secondary infection. Cultures were helpful in detecting truly infected eczematous eruptions. A simple Gram stain is made from the surface of the lesion to determine the presence of polymorphonuclear leukocytes plus bacteria indicating true infection. Bacteria alone indicate mere colonization and leukocytes alone indicate a cutaneous inflammation without bacterial infection. By these criteria, fourteen of thirty-nine patients who clinically appeared to have a secondarily infected atopic dermatitis showed a positive Kligman test (polymorphonuclear leukocytes plus bacteria). In primary cutaneous infections, topically combined hydrocortisone-oxytetracycline therapy is no more effective than oxytetracycline alone. In secondarily infected dermatoses, combined topical therapy with hydrocortisone-oxytetracycline is more effective than either ingredient alone. Smith[235] made assays on twenty-four hour urine specimens of volunteers who received 10 gm of hydrocortisone-free alcohol ointment which contained 250 mg of the active ingredient. The ointment was rubbed into the back, arms and thighs for ten minutes. Controls in which the base alone was employed were used. Smith found no significant change demonstrated in the urinary 17-ketosteroids and 17-hydroxycorticosteroids in this experiment.

Ingram and others[112] reported their experience with ACTH and cortisone in various skin disorders. Cortisone was used in the dose of 100 to 150 mg daily, while ACTH was given in doses of 50 to 100 mg daily. Eleven patients suffered with idiopathic exfoliative dermatitis and of these, nine were cured or the disorder controlled. Of seven patients with generalized psoriasis, six were improved during the first course of treatment but, in five, relapses occurred when treatment was discontinued. In patients with known sensitization dermatitis, the response to steroid hormone was often dramatic. Patients with seborrheic dermatitis, nummular eczema and varicose eczema showed less satisfactory responses. A decrease in sensitivity to patch test reactions was noted in several patients. The allergens were Cetrimide in two patients and adhesive plaster and sulfanilamide in one each. The reviewer notes that a reduction in a positive patch test reaction is not commonly seen with ordinary doses of steroid therapy. Frank et al[78] treated 144 patients with various dermatoses, comparing the effects of hydrocortisone-free alcohol, 1 per cent, hydrocortisone acetate, 1 per cent, and hydrocortisone acetate, 2.5 per cent. All these preparations were in identical bases. Efforts were made to treat symmetrical areas. Hydrocortisone-free alcohol is the pure hormone extracted from adrenocortical tissue and hydrocortisone acetate. The acetate is produced by partial chemical synthesis and has been avail-

able commercially for some time. The free alcohol was originally available in meager quantities but is now more freely available. Both the hydrocortisone-free alcohol and hydrocortisone acetate were found to be effective in such disorders as atopic dermatitis, contact dermatitis, seborrheic dermatitis, hand eczemas, nummular eczema, intertrigo, psoriasis, infectious eczematoid dermatitis and pruritus ani and vulvae. This study indicated that the hydrocortisone-free alcohol was slightly superior to the hydrocortisone acetate and the 2.5 per cent hydrocortisone acetate was not found to be sufficiently superior to 1 per cent hydrocortisone acetate to justify the additional expense to the patient.

Frank and Stritzler[77] reported on their experience with prednisolone and prednisone, formerly called metacortandrilone and metacortandracin, two new synthetic hormones which, milligram for milligram, possess greater anti-inflammatory effect and activity than cortisone or hydrocortisone. These agents do not produce sodium and fluid retention or potassium depletion to the extent found in the original preparations. Two hundred and fifty-six patients with various dermatoses were treated with prednisolone in the strength of 0.25 per cent to 0.5 per cent in an ointment of petrolatum and liquid petrolatum. Hydrocortisone in a concentration of 1 per cent in an identical base was used on a contralateral area whenever possible. Topical prednisolone has some therapeutic effect in those dermatoses that respond to hydrocortisone topically, but is less effective than a 1 per cent hydrocortisone ointment. Increasing the concentration of prednisolone from 0.25 per cent to 0.5 per cent does not increase the therapeutic effectiveness. Nine of the 256 patients found prednisolone ointment irritating. Sixty-seven patients with various dermatoses were treated systemically with oral prednisolone. Twenty-one patients in the group had been on hydrocortisone therapy prior to prednisolone administration and fourteen had been taking prednisone. In these patients, 5 mg of prednisolone was substituted for each 20 mg of hydrocortisone and prednisolone was substituted for prednisone, milligram for milligram. It was found that the systemic administration of prednisolone produced excellent therapeutic results in selected dermatoses. Milligram for milligram, prednisolone is approximately four times as effective as hydrocortisone. Patients treated with prednisolone can be placed on a nonrestricted diet, and hypertension and retention of sodium and fluids are not frequent complications. Robinson and associates[205] made comparison studies of thirty patients which indicated that 9-alpha-fluorohydrocortisone was as effective in 0.1 per cent concentration as 1 per cent hydrocortisone. It was not necessary to use a concentration greater than 0.2 per cent. The preferred base was a lotion or plasticized petrolatum. Careful laboratory studies following percutaneous absorption showed, after twenty-four hours, depressed sodium excretion, depressed eosinophil counts, elevated serum chlorides and serum sodium, depressed serum potassium, no weight change and a depressed urinary output. Sixty-eight patients were treated with neomycin or neomycin and bacitracin combined with the steroids. The antibiotics did not in any way interfere with steroid activity and were effective in controlling secondary pyogenic infection. Sodium retention and edema from topical application of fludrocortisone acetate were observed in twenty patients by Fitzpatrick and associates.[73] It was demonstrated that, for an average patient, when 0.25 per cent fludrocortisone acetate lotion was used, absorption of 50 mg of the active agent was possible.

Since clinical edema has been noted after oral ingestion of as little as 2 mg of this agent, the percutaneous route permits absorption of appreciable amounts of fludrocortisone acetate. This is especially true in an inflamed skin. Although less absorption is noted with improvement of the dermatitis from the topical application of this agent, its use is hazardous in patients with incipient congestive heart failure, toxemia of pregnancy, essential hypertension and nephritis. Livingood and associates[135] were in substantial agreement with other workers on the percutaneous absorption of fludrocortisone. It is estimated that a probable "safe" topical dose of fludrocortisone is 2 to 6 mg in a lotion and 5 to 12 mg in an ointment base. All patients using fludrocortisone should be checked frequently for weight gain and edema. In this study, ointments of 0.1 and 0.2 per cent, and lotions of 0.05, 0.1 and 0.2 per cent were used three to six times daily on the skin.

Eleven patients suffering with chronic dermatoses were given 60 to 80 mg of prednisone daily.[204] Following improvement, the original dose was given for two or three days, then gradually reduced by 5 mg every three or four days to levels that would keep the patients in satisfactory remission. Salt intake was not restricted. It was noted that several patients who had failed to improve with cortisone or corticotropin responded to prednisone. Two of the eleven patients had exfoliative dermatitis which had resisted all other forms of treatment and four in the series had severe, generalized atopic dermatitis. Improvement was seen in all within five to eight days. Laboratory studies were made on all patients and no significant changes noted with continued therapy. It was concluded that prednisone is apparently four to five times as active in the dermatologic conditions treated as cortisone, hydrocortisone or corticotropin. The reviewer notes that many of the complications of steroid therapy will appear with use of prednisone if comparable dosage is used. Robinson[206] reported a similar type of clinical experiment in ninety-six patients who were treated by the local application of 9-alpha-fluorohydrocortisone acetate. He found one unexplained unfavorable reaction to the preparation. In some cases a single application daily seemed to maintain patients in remission. In this study two patients with exfoliative dermatitis were treated systemically, starting with an oral dose of 12 mg of fludrocortisone daily. This was progressively reduced to a maintenance dose of 5 mg daily and to 3 mg in divided doses when unilateral edema of the right leg was noted in one patient. In another instance, a patient who had responded to a maintenance dose of 100 mg of cortisone was kept symptom-free by the substitution of 4 mg of fludrocortisone daily. Wright and others[268] used 9-alpha-fluorohydrocortisone acetate in sixty-four patients with various dermatoses in all of whom an inflammatory element was present. Previous studies had indicated that this preparation had about thirteen times the anti-inflammatory activity of hydrocortisone acetate. The preparation was found to be effective in atopic dermatitis with doses up to 9 mg per day orally for adults. Potassium depletion developed on doses of 4 mg per day. The usual side effects of hydrocortisone acetate were noted with this new preparation. The authors also used this preparation topically in an ointment or lotion base and noted the same good effects reported by Witten,[265] Sulzberger, Robinson[206] and others. The clinical effectiveness of the topical application of 9-alpha-fluorohydrocortisone acetate was compared with that of similar preparations containing hydrocortisone-free alcohol by Witten and others.[265] This

preparation is a derivative of hydrocortisone in which the 9-alpha-hydrogen atom has been replaced by a halogen. The base used was a plasticized petrolatum in one instance and a lotion in another. Concentrations employed were 0.5 per cent, 0.2 per cent and 0.1 per cent in each base. Sixty-two patients were used. They suffered from eruptions which commonly respond to topical steroids. Using simultaneous, paired comparison tests, the authors concluded that fluorohydrocortisone acetate was slightly more effective than hydrocortisone-free alcohol in topical therapy. There was no instance of allergic sensitization or of local or systemic damage from this preparation. The experience in this work also suggests that some patients are benefited more by one form of steroid than by another. A suspension of hydrocortisone in a shake lotion consisting of isopropyl alcohol, oil and an emulsified aqueous base was used by Lubowe[139] in the treatment of forty-nine patients with various dermatoses. Excellent results were obtained in atopic dermatitis and in contact dermatitis. The liquid hydrocortisone was just as effective as 1 per cent hydrocortisone ointment. A lotion containing 0.1 per cent of 9-alpha-fluorohydrocortisone was found to be as effective as 1 per cent hydrocortisone ointment. The 0.25 per cent preparation of this agent was found to be as effective as 2.5 per cent hydrocortisone ointment in relieving the pruritus and lessening the lichenification of neurodermatitis. In the bases used in this clinical work, there was no evidence of sensitization.

Eighteen patients receiving treatment with prednisolone or prednisone were given serial gastroduodenal roentgenologic studies at six week intervals by Bollet et al.[25] Peptic ulcers developed in three patients. There was no relationship between the time of the appearance of the ulcer and the duration of therapy or the total dose of the drug administered. It was of interest that the ulcers were not symptomatic, which indicated the need for close observation of these patients to discover sudden perforation or hemorrhage. The ulcers healed under a peptic ulcer regimen, and it was suggested that aluminum hydroxide gel be given routinely to patients receiving the newer steroids. Clinicians are sometimes puzzled by the recurrence of a dermatosis when steroid therapy is discontinued. This phenomenon was observed by Nexmand[164] who reported four patients presenting this complication of steroid therapy. The recurrence does not always resemble the original dermatitis. Nexmand observed groups of closely set papules in a skin which had become diffusely infiltrated symmetrically and also showed oozing. The original skin disease was masked by this exudative dermatosis which did not respond to prolonged topical treatment. The complicating dermatosis disappeared, however, on readministration of the steroids. Recurrence was noted when the steroids were discontinued. The original disease for which these patients were treated consisted of a contact dermatitis due to rubber in one, eczema of unknown cause in another and eczematids, pityriasis and atopic dermatitis in the third and fourth patients. It is suggested that steroids, once used, should be gradually reduced in dosage over a prolonged period of time to avoid this rebound effect. Dissemination of an exudative dermatitis complicated by Micrococcus (staphylococcus) bacteremia occurred after the administration of cortisone or corticotropin to two women and four men. Dougherty et al[58] reported that the hormones were administered to one patient for eczema, to one for exfoliative dermatitis, and to four patients for psoriasis. One patient in the group died. There is a distinct hazard of

lowered resistance to infection from the long administration of corticosteroids, especially in such conditions as chronic eczema, psoriasis and other nonfatal skin diseases.

Local injections of hydrocortisone acetate given at intervals of from eight to twenty days were used by Asboe-Hansen and others[15] in the treatment of thirty-eight patients with keloids. The age of the keloids was from six weeks to eight years. The total dose was from 35 to 725 mg, although a single dose varied from 5 to 50 mg, depending on the size and firmness of the keloid. In fifty-one keloids, the treatment resulted in softening or their complete disappearance. Examination of thirty-two keloids from two to eighteen months after treatment showed only one recurrence.

One hundred and ten infants and children suffering from contact or atopic dermatitis were treated with hydrocortisone ointment. Results were excellent in eighty-one and poor in twenty-nine. It is found, for example, that for the cheeks of a baby, provided there is not too much crusting, a 5 gm tube suffices for two daily applications for about six days. Hill[103] considered that it is best not to use hydrocortisone ointment with or without neomycin in infantile eczema when infection is present, even though there may be no actual pustulation. In two infants with crusted, oozy faces it was reported that the use of hydrocortisone ointment was associated with swelling of the face and marked lymph node enlargement in a few days. The addition of neomycin to the hydrocortisone did not seem to have any further favorable effect. Hydrocortisone ointment is most efficient in superficial scaly or erythematous areas. It is further stated, however, that there is still plenty of use for local remedies that have been valuable in the past in the treatment of infantile eczema. Most infants who have atopic dermatitis give strongly positive reactions to egg white, the majority of which are accompanied by circulating reagins and clinical sensitivity, according to Hill.[104] If the skin test is positive it is best to remove milk from the diet and to substitute one of the milk-free foods. These and other important points about the treatment of infantile eczema are collected in a recently published volume[105] by this authority. When cortisone therapy was introduced for the first time as a treatment for infantile eczema, the charge was made that the steroid would interfere with growth in infants and children. Hill[106] studied forty-three allergic children, eleven of whom had eczema and who received cortisone for periods varying from three to thirty months. The ages of the children ranged from six months to twelve years. The maximal dose given was 75 mg of cortisone per day and the usual maintenance dose ranged between 25 and 50 mg a day. In comparison with normal children not on cortisone for a similar period of time, it was shown that the retardation in growth in children taking moderate or small amounts of cortisone was very slight. It was recommended that the drug not be withheld in infants and children who require cortisone. Levin[131] suggested the use of ACTH gel for children with severe asthma. In contact dermatitis, ACTH gel may be used for three or four days or a steroid for five to eight days for severe poison ivy or oak dermatitis. In atopic eczema in infants and children, the hormones are indicated if a large part of the skin is affected. All this is symptomatic therapy and a search for the underlying cause by routine allergic investigation should be carried out.

A summary of the dermatologic principles involved in the management of pruritus ani was presented by Fromer.[81] Basic treatment was outlined

and includes the use of local and systemic measures. The local use of hydrocortisone ointment is effective in the patients who have "essential" pruritus ani. Anogenital pruritus is often a symptom of some definite dermatologic entity such as psoriasis or lichen sclerosus and treatment in these patients is directed to the management of the primary disease. Hydrocortisone acetate or free alcohol applied topically in a concentration varying between 1 and 2.5 per cent is a valuable symptomatic agent for the suppression or control of certain types of anogenital pruritus according to Turell.[255] Failures were seen in patients who were extremely tense and these may respond to the internal administration of Rauwolfia serpentina. Combination of hydrocortisone with an antibiotic was used in seventeen patients with pruritus and associated pyogenic infection. This combination was helpful without interfering with the antipruritic action of the hormone. Fludrocortisone acetate, 0.1 per cent and 0.25 per cent, has not shown any superiority to ordinary hydrocortisone in the treatment of fifteen patients with anogenital pruritus. An editorial in the *British Medical Journal*[64] expresses complete satisfaction with the advantage of hydrocortisone, applied locally, over the previous management of anogenital pruritus. The absence of side effects was noted and although relapses may follow withdrawal of hydrocortisone, relief helps to break a habit, gives the patient confidence and affords an opportunity to rest and regain health.

A fungating iododerma treated with hydrocortisone was reported by Aquilina and Bissell.[13] The patient was a man, aged thirty-seven, who presented a severe pustular dermatitis on the face, neck, back, trunk and extremities. The lesions had coalesced to form fungating and ulcerated nodules and plaques. There was a history of a cough mixture containing potassium iodide. Treatment was begun by giving hydrocortisone intravenously, 100 mg in alcohol diluted in 1000 cc of isotonic sodium chloride solution. The mixture was given slowly. In addition, the patient was given tetracycline, 250 mg every six hours. Salt solution compresses were used locally. By the fourth day the lesions had begun to subside. Further improvement was noted when hydrocortisone was applied topically in 0.1 per cent isotonic sodium chloride solution. The lesions flared when topical treatment was discontinued and again improved on reapplication of the wet dressings. Goudy and Masters[93] reported the successful use of cortisone in the treatment of black widow spider bites and bites of nonpoisonous spiders. It is their opinion that cortisone resulted in symptomatic relief and shortened the course of the recovery period. The reviewer notes that the severe granulomatous, infiltrative reactions following wasp and bee stings may be prevented by the early oral administration of corticosteroids.

Pinkerton[178] stressed the need for considerable caution in the use of ACTH or cortisone in treating agranulocytosis which is drug-induced. It has been suggested that steroids be withheld for at least seven days because the marrow frequently recovers in this time. Since the likelihood of infection is great in agranulocytosis, the well-known property of the steroids to mask infection looms high. (Why not steroids plus adequate dosage of wide spectrum antibiotics?—Reviewer.) Librach[134] reported three patients who developed erythema multiforme bullosa following ingestion of various drugs. The patients varied in age from four and one-half years to fifty-three years. The drugs incriminated in this group of patients included sulfonamides, penicillin, phenobarbital and sodium

hydantoinate, Dover's powder, Benadryl® and aspirin. The fifty-three-year-old man in this series died one week after the maximal intensity of the eruption appeared. All three patients were given ACTH and made an excellent response after the administration of this agent. The man who died was given ACTH intramuscularly. The reviewer has previously cited the instance of an aged thyrocardiac patient with a penicillin eruption who recovered fairly promptly with the administration of 60 to 100 mg of ACTH given intravenously in a slow drip. Renal insufficiency occurring in sarcoidosis is usually the result of hypercalcemia and nephrocalcinosis. A case of generalized sarcoidosis with hypercalcemia, nephrocalcinosis and renal insufficiency was reported by Gleckler.[90] Improvement in the general condition of the patient, with lowering of the serum calcium level to normal and improvement in the renal function, regularly follows the use of cortisone therapy. The effects have been maintained under treatment for a year. The mechanism involved in the lowering of the serum calcium level by cortisone in sarcoidosis is not clear. Clinically, pathologically and etiologically the Schönlein-Henoch syndrome has been linked with other allergic diseases—acute nephritis, rheumatic fever and polyarteritis nodosa. A fifty-five-year-old man, who suffered from Schönlein-Henoch syndrome and had an old history of rheumatic fever, was reported by Leese.[129] He was hospitalized because of joint symptoms and crops of purpura which persisted in spite of antihistamine therapy. In addition, further specimens of urine were found to contain hyaline and granular casts. This case therefore, represents three major allergic diseases: rheumatic fever, acute nephritis and the Schönlein-Henoch syndrome. The last mentioned was treated with corticotropin with dramatic improvement, and each relapse responded satisfactorily to corticotropin. He was finally placed on continuous treatment with this agent for nine months. Purpura was controlled and has remained controlled for nine months after administration of the drug was discontinued. Reiter's syndrome is a condition of undetermined etiology, manifested by urethritis, conjunctivitis and arthritis and in moderate and severe forms follows a characteristic course over a two- to four-month period. Skin manifestations are common in this syndrome. The skin lesions are called keratodermia blennorrhagica. Foxworthy and others[75] reported the use of ACTH and cortisone in ten patients with Reiter's syndrome. These agents were effective in suppressing symptoms but the course of the disease was not shortened by therapy.

Generalized scleroderma involves not only the skin but, more especially, important viscera. The scarcity of pulmonary function studies prompted Salomon and others[220] to record these studies including lung volume measurements, ventilation studies and determination of arterial blood gases before and after cortisone treatment in three patients with generalized scleroderma. Cortisone was given orally to each patient for thirty-five days, using a daily dose of 300 mg for three days followed by decreasing dosage and maintenance at 100 mg daily for twenty-seven days. Objective and subjective improvement of varying degrees occurred in all patients. The skin lesions were more responsive than the visceral involvement. Improvement of the skin lesions, however, was temporary and relapse occurred in all three patients four to six months after therapy was concluded. Pulmonary function was not significantly altered by this treatment. One patient started cortisone treatment in the fifth month of pregnancy and was delivered of a healthy infant. There was no untoward reaction either on the mother or child. Fourteen patients, varying

in age from twenty-three to seventy years, who were suffering from scleroderma were reviewed by Zion and others.[270] Duration of symptoms before treatment varied from three months to twelve years. Eight patients received both ACTH and cortisone and six patients were given cortisone alone. Results of treatment over variable periods of time showed that one patient with scleroderma of recent onset obtained a clinical and histologic remission while effective dosage of steroid was given. Three showed subjective relief of symptoms and partial improvement. Nine showed subjective relief of symptoms but little or no objective change. One patient was unimproved on steroid therapy. Patients suffering from scleroderma associated with Raynaud's phenomenon were not improved by steroid therapy. Prednisone was administered by Rodnan and others[209] to six patients with progressive systemic sclerosis (diffuse scleroderma), in oral doses of from 20 to 30 mg per day for uninterrupted periods of up to four and a half months. All patients experienced improvement in the skin with diminution in hyperpigmentation, swelling and tightness, commencing approximately one week after treatment was begun. Potent antirheumatic activity was shown in two patients with joint involvement. Improved ventilatory capacity was seen in one patient with pulmonary involvement. Gastrointestinal manifestations were not improved.

Malkinson and Wells[145] reviewed thirty-seven cases of periarteritis nodosa. These patients had been treated with ACTH or cortisone for extended periods of time. It was noted that three patients were well one or two years after one course of treatment; sixteen patients were moderately improved and two had been given cortisone in doses of 25 to 100 mg daily for three years. Four patients showed a poor clinical response in spite of steroid therapy and twelve patients died. Four of this latter group died of conditions unrelated to periarteritis nodosa. Clinical and laboratory responses are parellel in patients who respond to therapy. Skin lesions tend to clear, fever declines, blood pressure readings are lowered and improvement is noted in the sedimentation rate, albumin-globulin ratio and urinary findings. Some actions of corticotropin and cortisone are reviewed. These preparations inhibit antibody synthesis and reduce antibody levels. Repression of the tuberculin reaction as well as of the Shwartzman and Arthus phenomena has been noted. Rabbits sensitized to horse serum, when given steroids, are protected against vascular complications which ordinarily resemble periarteritis nodosa. In this disease a therapeutic paradox may be seen in which important organs with widespread arterial involvement show healing, with fibrous obliteration of vessels. This obliteration may also cause further vascular changes leading to hypertension. One patient in this series died of intra-abdominal aneurysmal hemorrhage during cortisone therapy. It is to be remembered that adrenal steroids may have little or no beneficial effect on impaired renal function and sometimes their administration may be detrimental in patients with renal involvement. Six patients with disseminated lupus erythematosus and three patients with periarteritis nodosa were treated with Meticorten® by Steinberg and Roodenburg.[239] One patient with periarteritis nodosa died while under treatment. Autopsy showed extensive arterial involvement, both visceral and peripheral. The lack of inflammatory process in the diseased arteries suggests that better results would have been obtained if treatment had been started in the early phase of the disease. Six patients with disseminated lupus erythematosus

had previously been treated with either cortisone or corticotropin. All six have maintained improvement with Meticorten. The impression following these studies is that the patients have done much better with Meticorten.

MISCELLANEOUS ALLERGIES

Leider[130] reviewed the modern concepts of the allergy of infection. This is a fundamental paper with statements, speculations and syntheses of our present clinical knowledge of this subject. He refers to Sulzberger's "Dichotomy" dividing the infectious disease into two large groups. Group 1 includes primarily toxic infectious diseases. Pathogens of this group regularly produce soluble exotoxins. Examples are the microorganisms of diphtheria, tetanus, botulism, scarlatina, streptococcal and staphylococcal infections, and so forth. Skin reactions to a characteristic product in patients before adequate exposure in this group are positive and after adequate exposure are negative. Group 2 includes primarily sensitizing infectious diseases. Pathogens of this group produce no regularly demonstrable toxins but have other allergenic principles which are sensitizing. Examples are the microorganisms of tuberculosis, deep and superficial mycoses, leprosy, syphilis, lymphogranuloma inguinale, leishmaniasis, and so forth. Skin reactions in patients of this group are negative before and positive after adequate exposure. These two divisions are made according to host response to the products of the causative microorganisms before and after infection or adequate exposure. The diseases of the two groups show marked differences between them and marked similarities to each other within each group regardless of the causative microorganisms. Diseases caused by the toxin-producing microorganisms are acute, fulminating processes caused by the primarily injurious nature of poisons. Recovery and immunity are allergic events. Near perfect protection against these diseases can be produced artificially by proper use of toxins. Diseases caused by microorganisms that do not produce toxins are protracted and varied affairs that result from allergic transformations. Recovery and immunity are not clear-cut conditions but depend on development of allergic transformations that are favorable to the host or on disappearance of allergens through disappearance of microorganisms. Some degree of protection can be induced by producing some part of the disease process, usually the initial changes, by subclinical doses of the microorganisms or by attenuated or related species of them that are allergenic but not virulent.

Studies were made by Cole and Favour[44] correlating plasma protein fractions, antibody titers and passive transfer of delayed and immediate cutaneous reactivity to tuberculin PPD and tuberculopolysaccharides. This was accomplished by using large volumes of immune guinea pig plasma and injecting separate fractions intraperitoneally into normal guinea pigs. Passive transfer of these fractions was then accomplished and the animals were skin tested with a variety of derivatives from the tubercle bacillus. Antibody to tuberculopolysaccharide could be demonstrated only in fraction II (gamma globulin). This fraction passively transfers anaphylaxis in urticarial type skin reactivity to tuberculopolysaccharide. Antibody to tuberculoprotein was found exclusively in a new plasma fraction called fraction IV-10 and this is a part of fraction IV (alpha globulin) and to a lesser extent V (albumin). In a discussion of this important work, Baer and Witten (p. 411 *Yearbook of Dermatol-*

ogy,[269] 1955-1956) comment that, while the antibody of the tuberculopolysaccharide is contained in the gamma globulin fraction and the antibody to the tuberculoprotein is contained in the alpha globulin fraction, the plasma fractions containing these two antibodies when combined completely inhibit the passive transfer of the delayed forty-eight hour type skin sensitivity. This suggests that an often undetected urticarial and anaphylactoid sensitivity frequently accompanies eczematous hypersensitivity. It may also explain the failure of passive transfer of eczematous allergic sensitivity in man by the presence of an inhibiting plasma fraction against urticarial hypersensitivity.

Autosensitization is a frequent phenomenon in varicose and postthrombotic eczemas. Haxthausen[102] noted eighty-eight instances of secondary eruptions in 235 cases of varicose and postthrombotic eczemas. In a control group of eczemas of other origin, autosensitization occurred in only 4 per cent of the cases. Generalized eczemas are marked by a remarkable symmetry which suggests hematologic spread. When the primary eczema is treated adequately the secondary eruptions usually disappear spontaneously. Goldman[91] described bacterial dermatitis in external otitis. Aside from cleansing and affording relief from pain, the local administration of antibiotics and chemotherapeutic agents is the treatment of choice, whether it be in the form of powder, ointment or aqueous solution. The need for routine cultural and microscopic examinations and tests for antibiotic sensitivity cannot be over-emphasized in this disease. There is a great variation in susceptibility of the Micrococcus and Gram-negative bacilli to antibiotics, and sensitivity tests are helpful. Since *Ps. aeruginosa* is isolated frequently from infections of the external auditory canal, polymyxin might be used as a therapeutic agent until reports of sensitivity studies are returned. The nonbacterial or eczematoid type of external otitis is a more complex problem. It is the impression that this disease is a manifestation of local hypersensitivity to *M. pyogenes* var. *aureus A.* Thus in addition to local therapy hyposensitization with autogenous vaccine or toxoid is suggested. Schnitzer[225] investigated the effect of systemic disturbances in the pathogenesis and course of eczema. In a number of patients with matchbox dermatitis he found that 50 per cent suffered from peripheral alterations of the vascular and nervous system, including diabetes, hypertension, gastric ulcer and chronic nephritis. Schnitzer rejected the belief that bacterial sensitization was a factor in various intertriginous and varicose eczemas since positive reactions to ubiquitous bacteria may occur in healthy individuals. Specific and nonspecific positive reactions can hardly be differentiated. He assumed that active internal disorders can influence the pathogenesis and course of eczema. This influence may take place by means of nonspecific mechanisms, for example, changes in histamine blood levels at the beginning of the menstrual flow, after large intravenous doses of vitamin B_2, or changes in systemic reactivity during infectious diseases and pregnancy. The development of enlarged axillary nodes in two infants within a few days after immunization with whooping cough vaccine, diphtheria and tetanus toxoids is described by Lapin and Tuason.[127] Biopsy in both cases was interpreted as showing a hyperplastic response in the lymph nodes to the immunization antigens. In neither case was there any fever or other signs of a generalized reaction nor was there any marked redness or tenderness over the swellings. The role of regional glands after im-

munization with pneumococcic and streptococcic vaccines has been reported previously. It is known that the introduction of an antigen into tissue causes an inflammatory reaction and this may lead to hemorrhage, necrosis, suppuration or other undesirable changes locally or in the regional lymph nodes. These changes begin to appear on the third or fourth day and reach their highest peak of change on the sixth or seventh day.

Numerous cases of periarteritis have been attributed to sensitization to drugs including sulfonamide, sulfathiazole, thiouracil, thiourea, penicillin, organic arsenicals, dilantin, aspirin and Lugol's solution. The lesions in some of these instances which differ in some respects from those of classic periarteritis nodosa have been called hypersensitivity angiitis. Edge and his associates[62] reported the case of a thirty-three-year-old housewife who was treated for suppurative otitis media with systemic penicillin. This had to be discontinued after a few days because of a fever and a general rash. Shortly after this right-sided pleuritic pain developed which persisted. A roentgenogram of the chest showed two dense, homogeneous rounded opacities in the lower zone of the right lung, and she was treated with streptomycin and Isoniazid. Fever and rash continued, the patient's condition deteriorated in spite of corticotropin therapy and she died about eight weeks after therapy with streptomycin and Isoniazid was begun. At postmortem examination a generalized hypersensitivity angiitis was found and it was postulated that the opacities seen in the chest roentgenogram were due to arteritis which had developed previously. The importance of recognizing collagen disease is emphasized. In discussing this case, Rose[211] stated that cortisone has been used extensively in the treatment of polyarteritis and with the use of adequate dosage (which may mean 500 mg a day or even more) it prevented the appearance of new lesions in nearly all cases. A morphologic pattern characterized by eosinophilic leukocytes invading the tissue and by fibrinoid necrosis destroying the walls of blood vessels is a type of vasculitis recognized as periateritis nodosa since 1886. Although this disorder varies in degree, a number of related vascular conditions were described by Szymanski.[247] A differentiation was made between cutaneous allergic vasculitis, systemic allergic vasculitis, granulomatous allergic vasculitis and periarteritis nodosa. It has been shown, for example, in periarteritis nodosa that only one third of the cases display signs and symptoms suggestive of sensitivitv. Allergic vasculitis and periarteritis nodosa are now regarded as two distinct diseases and it is claimed that they can be distinguished clinically and microscopically. Cutaneous allergic vasculitis is limited to the skin, blood eosinophilia is common, and the arterioles, venules anl capillaries of the superficial coreum are affected. The course is mild, and the extremities are chiefly affected. Papules, pinpoint vesicles or small hemorrhagic crusts may be seen. Sensitivity to a drug is the usual basis for the development of this eruption. Systemic allergic vasculitis (hypersensitivity angiitis) is characterized by widespread involvement of lungs, spleen and skin. The kidneys show a peculiar type of necrotizing glomerulonephritis. Eosinophilia is rare and arterioles, venules and small arteries of the collagen type are affected. This condition runs a fulminating course from a few days to a few weeks and is usually serious and fatal. If the condition is suspected, steroids may be life-saving. Granulomatous allergic vasculitis is a widespread condition exhibiting cutaneous and systemic manifestations. It is often fatal but has a slower course than

systemic allergic vasculitis. A group is reported which was associated with asthma. The patients show fever, hypereosinophilia and symptoms of cardiac failure, renal damage and central nervous system injury. Recurrent bouts of pneumonia are found in nearly every case. Hypertension is frequent and abdominal pain and bloody diarrhea are common complaints. Skin lesions are multiform in character and nonspecific, including erythema, maculopapules, pustules and purpura. Polyarteritis nodosa affects the small and medium sized arteries. Eosinophilia is common and systemic involvement includes heart, kidney, gastrointestinal tract and pancreas. The lungs and spleen are not involved. The disease is of long duration, persisting for months or years, with fever, weakness, headaches and muscular pains predominating. Although steroids are the most effective therapeutic agents available, it is of interest that healing consequent to treatment may be followed by vascular obliteration and multiple infarction. Renal failure and hypertension may result from such an extensive healing effect. Fifteen patients with acute vascular purpura are presented by Kreidberg and others.[123] Infection preceded the onset of purpura in all cases. The fifteen patients were children; all had purpura, fourteen had joint symptoms, eight had gastrointestinal symptoms and three died of renal failure. Three patients were allergic (asthma); all responded to ACTH. The hemolytic streptococcus is probably the agent that sensitizes and triggers the response.

Stüttgen[246] believed that bullous purpura developing during a general hemorrhagic inflammation of the skin and mucous membranes may be due to subacute sepsis with infectious-allergic symptoms. He described six patients with hemorrhagic bullae which were most pronounced on the feet, hands and nose, where the circulation is most labile and subject to static factors. Hemorrhagic blisters and ulcerations were frequent. Clinically, distinguishing between an allergic reaction and the Shwartzman-Sanarelli phenomenon may be difficult, particularly before necrotic changes appear. Erythema multiforme is described as a symptom complex rather than an etiologic diagnosis.[185] A search must be made for bacterial or virus infection or ingestion of food or drugs to which the patient may react. Antihistamines, antibiotics and steroids are effective but treatment must be individualized.

Similar points of acute rheumatism, acute nephritis and anaphylactoid purpura are noted by Lewis.[133] Attention is also drawn to the fact that upper respiratory tract infection associated with hemolytic streptococci sometimes preceded these conditions. The frequency of this association suggested bacterial hypersensitivity as an etiologic factor. In studying a large group of children with anaphylactoid purpura, nephritis and rheumatism, the author thought that the evidence supported a close relationship between anaphylactoid purpura and acute nephritis and a bacterial hypersensitivity as a major causal factor in all three conditions. A sharp rise in the number of cases of anaphylactoid purpura is to be seen in the spring and in autumn, which suggests a relationship with respiratory tract infections. Gardner and Diamond[84] studied four women who reported an abnormal response to bruising. This was characterized by local pain, swelling and extension of bleeding into adjacent areas, often to a serious extent. Studies on these patients indicated that they had an abnormal reaction to their own red cells when they have penetrated the usual channels and have entered extravascular tissues. Intradermal tests were made to 10 per cent hematocrit concentrations of red cells and these tests

were negative. Severe reactions, however, followed concentrations of 50 to 80 per cent. The reactions were characterized by painful, erythematous, indurated areas similar to the spontaneous lesions. No specific therapy is available for this type of purpura. Two patients had splenectomy with no improvement in one and only temporary improvement in the other. It was thought that intradermal desensitization would be helpful but severe reactions to the intradermal injections developed. The authors believe this autosensitization mechanism may explain the pathogenesis of lupus erythematosus, some forms of acquired hemolytic anemia and thrombocytopenic purpura.

Skin lesions are found in about 25 per cent of cases of periarteritis nodosa.[4] The best known manifestation is the subcutaneous nodule although this is found in only 16 per cent of all cases. Nodules are commonly found along the course of small arteries, particularly on the legs but also on the wrists, forearm, angle of the jaw, forehead and neck. Erythematous macules are common, particularly on the extremities, and they may become purpuric or lead to a secondary blister resembling erythema multiforme in appearance. Purpura may actually be massive. Necrosis of the skin may develop and lead to formation of ulcers. These ulcers may be severe, resembling those seen in "phagadenic" ulceration which occasionally accompanies ulcerative colitis. Lesions of the mucous membranes are also seen; they may be papular or nodular lesions, transient blisters, necrotic ulcers or massive infiltration. Five categories of necrotizing arteritis are classified by Zeek (Zeek, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis. New England J. Med., 248:764, 1953); hypersensitivity arteritis, allergic granulomatous arteritis, rheumatic arteritis, temporal arteritis, and classic periarteritis nodosa. Many of the nodular and necrotizing lesions formerly diagnosed as tubercles are less confidently regarded as manifestations of tuberculosis. Some are called "nodular vasculitis" whereas Gougerot's school calls them "nodular cutaneous allergides."

Atabrine and its analogues have found a wide field of usefulness in light sensitivity dermatoses, lupus erythematosus and in a group of heterologous dermatoses such as psoriasis and lichen planus. Gaté and others[85] reported the use of Nivaquine in a patient with periarteritis nodosa. This preparation is similar to the American chloroquine and was used in combination with vitamin C, chloramphenicol and Hydergine. No improvement had followed the extensive use of steroids. In April 1954, the patient was given seven tablets of 0.1 gm of Nivaquine daily. Improvement of the cutaneous manifestations of periarteritis nodosa followed, and this was maintained when the dose was reduced to three tablets given on alternate days. Although Nivaquine was given with a number of other preparations it seems probable that this was the effective agent in producing improvement. A complete discussion of polyarteritis nodosa in reference to symptoms, diagnosis and treatment was reported by Lovell and Rose.[137] It was stressed that many patients in whom the disease developed were already suffering from chronic respiratory infection, acute respiratory infection or rheumatoid arthritis. Early in the disease the prominent features are fever, tachycardia, weight loss, diffuse aching and tenderness of the muscles. As a rule, the course is one of increasing deterioration. Findings include an increased sedimentation rate and hypoplastic anemia, and some degree of eosinophilia is common, especially when pathologic changes in the lung are present. Globulins are

increased. As in lupus erythematosus disseminatus, kidney involvement is frequent and of eight patients in this series who died, two had malignant hypertension. The manifestations of skin findings in polyarteritis depends upon the depth and size of the affected arteries. Involvement of subcutaneous arteries produces nodules with normal overlying skin. More commonly noted are superficial papules which appear in crops associated with purpura, and usually on the extremities. Infarction of vessels in the dermis often leads to hemorrhage, vesiculation and central necrosis with ulcer formation. A purplish reticulation of the skin is often seen in cutaneous polyarteritis. The course of eight patients who were given steroid therapy was followed for a period of five years. Two have died, three were still using cortisone and three had gone into a remission of the disease.

O'Leary[169] discussed the case of a thirteen-year-old white girl with dermatomyositis. This condition is a polymyositis with a variety of cutaneous pictures. In some there are no skin lesions but muscle involvement is pronounced, while in others the degree of muscle involvement is minimal and the changes in the skin are extensive. Creatinine estimations do not help a great deal in recognizing this condition, since the creatinine level varies greatly depending on the diet and because there are normal variations from person to person. A muscle biopsy is often a misleading diagnostic effort. The pathologic picture of dermatomyositis is not classic and since there may be patchy involvement of muscle it is quite possible that the biopsy specimen may reveal only normal tissue. An electromyographic study, however, is much more helpful, as these examinations distinguish muscles with neuron involvement from those with primary myopathies. The use of electromyographic studies has uncovered many patients with polymyositis who otherwise would have gone undiagnosed. Cortisone administration may result in amelioration to some extent for a short time, but it is not curative. Caldwell[33] divided dermatomyositis into three types: first, a chronic, progressive dermatomyositis which is present in the acute form in children but more commonly an insidious onset leads to irreversible changes before the disease is clearly recognized; second, a symptom complex associated with coincident visceral neoplasm. Since the first paper in 1935, fifty recorded examples of acute dermatomyositis associated with neoplasm including Hodgkin's disease have been reported. Skin lesions may closely resemble disseminated lupus erythematosus. The third type is a polymyocytic form of polyarteritis nodosa. This is a hyperacute fulminating or self-limiting condition commonly seen in young adults, usually associated with sulfonamide therapy.

Patients suffering from ulcerative stomatitis, herpetic stomatitis and other painful lesions of the mouth in association with some skin lesions can be made more comfortable by a mouth wash containing a local anesthetic. In this form Benadryl and pyribenzamine have been effective mouth washes, producing satisfactory relief of pain so that patients may be given adequate diets. Labelle and Tislow[124] screened about seventy compounds for antihistamine activity. Chlor-Trimeton was found to have a local anesthetic activity equal to that of procaine but less than that of Benadryl or pyribenzamine. Buffering of the solution to pH 7.4 increased the local anesthetic potency of all the antihistamines. Chlor-Trimeton, 0.25 per cent concentration, was used in rabbit eyes daily for thirty days without producing irritation. A 10 per cent solution given subcutaneously was

tolerated by guinea pigs. The etiology of aphthous or so-called dyspeptic ulcer still remains obscure in spite of the considerable amount of work done on the subject.[7] They are now thought to have no connection with dyspepsia and are seen more frequently in females than in males. The ulcers are formed as a result of the breaking down of vesicles resulting from intra-epithelial edema of the stratum granulosum of the oral mucosa. There is some evidence that the ulcers may be allergic in origin and on this basis antihistamines have been employed and success has again been reported. The treatment of painting the ulcers with a caustic cannot be recommended, since this usually merely prolongs the healing process and does not prevent the formation of additional ulcers. In answer to a question regarding the correlation or connection between chemical change in the saliva and the occurrence of canker sores, it is stated that at the present time there is no known specific noxious agent or chemical change in the saliva that would cause aphthous stomatitis starting on the papilla of the parotid duct or near the sublingual ducts.[191] No such agent has been demonstrated except in heavy metal poisoning, such as mercury and lead. It is more likely that the local lesions in the mouth represent a focal manifestation of systemic disease. Such lesions have actually been demonstrated at sigmoidoscopy, in allergy, leukemia, agranulocytosis, uremia and tuberculosis. At times intestinal symptoms are completely absent, but usually abdominal pain and diarrhea are present in the case of ulcerated lesions and sigmoidoscopy reveals the same type of inflammatory reaction as seen in the mouth. The mechanism in the bowel is the transfer of the noxious agent in the blood stream from a different focus and excreting it through the wall of the bowel into the lumen. A similar mechanism may explain the lesions in the mouth.

The Stevens-Johnson syndrome is a skin eruption resembling erythema multiforme, with lesions of the mouth, conjunctivae, genitalia and anus. It was first described in 1922. It is suggested that the eruption may be due to hypersensitivity either to infection or to drugs. Hahn[99] reported the development of this syndrome in a nine-year-old boy; in addition, there was gross surgical emphysema stretching from the neck to the lower abdomen. On the day after admission the emphysema had spread downward to the groin and into the upper parts of the thighs. Large pockets of air were palpable under the skin in the region of the lower ribs. The boy suffered a stormy, febrile course but ultimately responded to antibiotics, plasma given intravenously and supportive therapy. The case represented a severe form of the Stevens-Johnson syndrome in which the skin, mucous membranes and respiratory system were all heavily affected. The likely explanation for the surgical emphysema was the trapping of air behind an obstruction such as is seen in pertussis, influenza or measles and in bronchial asthma where valvular obstruction of terminal bronchioles may be produced by mucous plugs or by inflammatory edema of the lining mucosa. Alveolar air trapped behind the obstruction may be forced into the interstitial spaces of the lung by expiratory pressure by way of the mediastinum where the air may then escape into the tissues of the neck.

Ansell[5] reported three cases of accidental vaccinia. The first patient was a woman who had a background of eczema, asthma and urticaria. The second patient stated that her baby had been vaccinated eleven days before the onset of her eruption. The patient had never been vaccinated but she too had a history of eczema. The lesions were fairly uniform, erythe-

matous, papulovesicular and pustular eruptions involving the face, scalp, neck, breasts, antecubital and popliteal areas and several fingers. The first patient was exposed to her son who had been vaccinated about two weeks before the onset of her illness. The dermatitis resolved slowly. It was concluded that patients with skin lesions who have never been vaccinated or who have not recently been vaccinated should avoid contact with newly vaccinated persons especially if they have a background of previous atopic dermatitis. Bullous prurigo is a rare skin abnormality which occurs in children of eighteen months to three years. The bullae are limited to the skin of the legs and soles and are not surrounded by an inflammatory halo. They are usually 2 to 30 mm in diameter. The eruption persists for several weeks to a month but it tends to recur. As a rule certain foods, such as chocolate, cocoa, eggs and fish can be incriminated as exciting agents. Carteaud and associates[38] stated that other bullous skin diseases must be differentiated and often the condition must be differentiated from insect bites, bullous drug eruptions and dermatitis herpetiformis which usually appears after puberty. Treatment consists in elimination of offending foods and symptomatic treatment. The local application of antipruritics, gentian violet or eosin is recommended.

Tuft and others[253] reported the case of a male chemist, aged twenty-seven, who had a number of allergic complaints which were proved clinically to be due to sensitivity to foods high in sulfur content. Skin tests with these foods were negative. Similar symptoms followed inhalation of hydrogen sulfide vapors. It has been shown that sulfur amino acids in the body may act by first being converted into hydrogen sulfide or methylmercaptan. This is accomplished with the aid of a normal intestinal flora, which may be inhibited by antibiotics. The patient was given aureomycin and sulfasuxidine for twenty days and during this period ingestion of egg produced no symptoms. Apparently, in the absence of a suitable flora the sulfur was not metabolized to produce an antigen familiar to the patient's immune mechanism. After the antibiotics were discontinued, egg again caused difficulty. This case report poses a number of questions as to whether the patient's abnormal allergic symptoms represented a true allergic reaction or they resulted from the biochemical alteration of the food in the intestine or tissues. If reactions are due to biochemical changes, involving the intestinal flora, the inconsistencies often seen in food allergies could be explained.

Insulin hypersensitivity or allergy is not a common clinical finding and actual anaphylactic shock is extremely rare. Rose and Barron[210] reported the case of a forty-year-old man who was given insulin, first intramuscularly and then intravenously as part of a routine insulin coma therapy. On the tenth intravenous injection of the same batch of soluble insulin, the patient coughed and then retched. This was accompanied by severe bronchospasm and the patient became pallid and cold. An intravenous injection of epinephrine tartrate, 1:1000, was given slowly and general treatment for shock was begun. For four hours his condition remained critical; with the continued use of epinephrine, stimulants and intravenous infusion of dextrose he subsequently recovered. Following recovery, an intradermal skin test gave a strong positive reaction. All other types of insulin tested also gave positive skin reactions. Saline controls were negative as were intradermal solutions of pig, beef and mutton proteins. About a month later passive transfer of sensitivity was

attempted using four healthy nonallergic subjects; three gave positive reactions and one a slight positive reaction.

Perlman[176] discussed immediate and delayed (serum type reactions) following insect bites. Cross reactions between bee and wasp sensitivity are common but not clearly understood. The literature concerning the chemistry and immunology of bee and wasp stings was reviewed. Evidence of the allergic nature of the reactions was presented. Desensitization or immunization appeared valuable in seven patients who were treated by the author. A patient need not have an asthmatic or atopic background to develop alarming anaphylactoid reactions from insect bites. Epinephrine, antihistamines and corticotropins are the most useful agents for therapy. Mueller and Hill (Mueller, H. L. and Hill, L. W.: Allergic reactions to bee and wasp stings. New England J. Med., 249:726, 1953) stated that desensitization may be very hazardous in certain individuals even though the preliminary injections have not been followed by reactions. Perlman stated that insect sensitivity may persist for years and the decision to immunize should depend on the severity and frequency of the reaction, and the location and occupation of the individual in relation to future stings. Due to the injected bee venom, bee stings may result in a local reaction, a more generalized allergic reaction, or both.[11] The sting should be gently removed and a weak alkaline solution applied. For the severe allergic reactions, angioedema, severe dyspnea, collapse or unconsciousness, 1:1000 epinephrine should be given in doses of 5 to 10 minims and repeated as necessary. Hyposensitization may be successfully accomplished using a mixed bee venom antigen available from commercial firms. Necrosis following spider bite is rare with the common black widow spider, Latrodectus mactans, which causes most poisonous spider bites in this country. Necrosis is characteristic of the bite of the large, hairy tarantula, especially the Lycosa raptoria of Brazil and the Glyptocranium gasteracanthoides of Peru.[194] The amount injected by the black widow spider is so small and so rapidly penetrates the tissues that it is doubtful whether any good may be served by such strenuous local treatment as application of corrosive chemicals and incision and scarification at the site of the bite. Necrosis may occur as a result of infection coincident with or following the bite of the black widow or other spiders. These insects usually inhabit relatively dirty places, and pyogenic cocci or anerobic spore-forming bacteria such as are responsible for gas gangrene may infect the puncture point. Simple cleansing of the bitten area and the application of mild antibacterial agents such as alcohol or hydrogen peroxide are usually to be preferred. No serum against the necrotizing venoms of spiders is at present available in the United States. Parsons[170] described a forty-one-year-old man who had been bitten by bedbugs and this was followed by sudden waking and a choking sensation accompanied by swelling of the arm and neck. Shortly afterwards he collapsed. A diagnosis of coronary disease was made. Several months after he recovered, a single bedbug bite was allowed. In one minute a positive reaction appeared and in fourteen minutes a moderate drop in blood pressure and generalized pruritus occurred. Relief was obtained by injection of 0.1 cc. of 1:1000 epinephrine at the site of the bite.

Further studies with Piromen[97] were made by Guy and Green who used this agent as adjunctive therapy in the management of atopic eczema, chronic urticaria, lichen simplex chronicus and nummular eczema. Sub-

cutaneous administrations of Piromen were made in doses of 4 to 10 gamma per injection. No added advantage could be found by using the intravenous route. No apparent side effects were associated with subcutaneous administration of Piromen. The preparation was used over a two-year period and the study was carefully controlled since the clinicians were unaware at the time of injection whether they were using an active agent or a saline control. Of twenty-eight patients treated with this agent, seventeen improved, seven showed no change and four became worse. Of the fifteen controls, only two improved, eight showed no change and five became worse. No side effects were apparent when the drug was given subcutaneously in doses up to 20 gamma.

Ungar[256] concluded that the addition of vasoconstrictors had a considerable enhancing effect on the antigenic action of diphtheria toxoid. Epinephrine hydrochloride is stable only in an acid medium and cannot be kept in contact with a toxoid for any length of time. Ephedrine and benzedrine, being stable at neutral pH, can be mixed with the toxoid and stored at a suitable temperature. Benzedrine hydrochloride was used in a dilution of 1:250, and ephedrine was used in a similar dilution.

REFERENCES

1. Alden, H. S.: Industrial dermatitis. Ann. Allergy, 13:695, 1955.
2. Allison, F., Jr.; Smith, M. R.; and Wood, W. B., Jr.: Studies on the pathogenesis of acute inflammation. I. The inflammatory reaction to thermal injury as observed in the rabbit ear chamber. J. Exper. Med., 102:655, 1955.
3. Annotations. Chrome dermatitis. Lancet, 2:603, 1955.
4. Annotations. Skin lesions in periarteritis nodosa. Lancet, 1:854, 1955.
5. Ansell, H. B.: Accidental vaccinia. J. Maine M. A., 46:223, 1955.
6. Any Questions? Anaphylactoid reactions to penicillin. Brit. M. J., 2:1281, 1955.
7. Ibid: Aphthous ulcers. Brit. M. J., 1:242, 1955.
8. Ibid: Risk of agranulocytosis with sulphonamides. Brit. M. J., 1:55, 1955.
9. Ibid: Sensitization to streptomycin. Brit. M. J., 1:1295, 1955.
10. Ibid: Treatment of agranulocytosis following drugs. Brit. M. J., 1:55, 1955.
11. Ibid: Treatment of bee stings. Brit. M. J., 1:1296, 1955.
12. Ibid: Urticaria and malaria. Brit. M. J., 1:118, 1955.
13. Aquilina, J. T., and Bissell, G. W.: Fungating iododerma treated with hydrocortisone. J.A.M.A., 158:727, 1955.
14. Arthur, R. P., and Shelley, W. B.. Experimental evidence for enzymatic basis for itching in man. Nature, 175:901, 1955.
15. Asboe-Hansen, G.; Brodthagen, H.; and Zachariae, L.: Behandling af keloider med lokale injektioner af hydrocortison-acetate. Ugesk. f. laeger, 117:1428, 1955.
16. Baer, R. L.: Formaldehyde. Letters Internat. Corres. Club Allergists, 18:31, 1955.
17. Baer, R. L.; Serri, F.; and Weissenbach-Vial, C.: Studies on allergic sensitization to certain topical therapeutic agents. Arch. Dermat., 71:19, 1955.
18. Barr, D. P.: Hazards of modern diagnosis and therapy—the price we pay. J.A.M.A., 159:1452, 1955.
19. Beckett, A. G., and Foxell, A. W. H.: Thrombocytopenic purpura associated with oxytetracycline therapy. Lancet, 1:1053, 1955.
20. Benjamin, F. B.; Beerman, H.; and Shelley, W. B.: Allergic contact dermatitis due to histamine-releasing drug 48-80. Arch. Dermat., 71:190, 1955.
21. Berger, A. J., and Eisen, B.: Feasibility of skin testing for penicillin sensitivity. J.A.M.A., 159:191, 1955.
22. Bettley, F. R.: Industrial and domestic dermatoses. Proc. Roy. Soc. Med., 48:505, 1955.
23. Binns, T. B.: Correspondence. Desensitization of nurses allergic to penicillin. Brit. M. J., 2:680, 1955.
24. Bluefarb, S. M.: Common hand eczemas. Ann. Allergy, 13:398, 1955.
25. Bollet, A. J.; Black, R.; and Bunim, J. J.: Major undesirable side-effects resulting from prednisolone and prednisone. J.A.M.A., 158:459, 1955.

26. Bookman, R.: Problem of eczema. J.A.M.A., 159:1275, 1955.
27. Borrie, P.: A purpuric drug eruption caused by carbromal. Brit. M. J., 1:645, 1955.
28. Bourne, G.: Medical Memorandum. Reactions to intramuscular iron. Brit. M. J., 2:305, 1955.
29. Brown, E. A.: Problems of drug allergy. J.A.M.A., 157:814, 1955.
30. Brown, E. A.: The question of reactions to mercurial diuretics. Ann. Allergy, 13:131, 1955.
31. Brunsting, L. A.; Reed, W. B.; and Bair, H. L.: Occurrence of cataracts and keratoconus with atopic dermatitis. Arch. Dermat., 72:237, 1955.
32. Burrage, W. S.; Ritchie, A. C.; Mansmann, H. C., Jr.; Irwin, J. W.; and Russfield, A. B.: The use of cortisone and hydrocortisone in allergy. Ann. Int. Med., 43:1001, 1955.
33. Caldwell, I. W.: Correspondence. Dermatomyositis. Brit. M. J., 1:1477, 1955.
34. Calvert, R. J., and Smith, E.: Penicillin anaphylactoid shock. Brit. M. J., 2:302, 1955.
35. Campbell, P. E.: Sudden death in labor following an injection of penicillin. Brit. M. J., 1:87, 1955.
36. Cannemeyer, W.; Thompson, J. R.; and Lichtenstein, M. R.: Severe para-aminosalicylic acid hypersensitivity. Blood and lymph node studies. Blood, 10:62, 1955.
37. Carrie, C.: The efficacy of protective skin ointments. Hautarzt, 6:363, 1955.
38. Carteaud, A.; Hewitt, J.; and Tabernat, J.: Le prurigo bulleux. Presse méd., 63:186, 1955.
39. Chelating agents. Lancet, 1:754, 1955.
40. Church, R.: Hydrocortisone ointment in the eczemas. Brit. M. J., 1:517, 1955.
41. Clark, H. G.: Alkaline treatment of acute allergic shock. J. Michigan M. Soc., 54:1198, 1955.
42. Clein, N. W.: A new antihistamine for treatment of various allergic manifestations. Ann. Allergy, 13:163, 1955.
43. Coggins, R. P.: Correspondence. In reply to "A defense of sodium dehydrocholate." New England J. Med., 252:552, 1955.
44. Cole, L. R., and Favour, C. B.: Correlations between plasma protein fractions, antibody titers and passive transfer of delayed and immediate cutaneous reactivity to tuberculin PPD and tuberculopolysaccharides. J. Exper. Med., 101:391, 1955.
45. Coleman, M.: Correspondence. Skin testing for penicillin sensitivity. J.A.M.A., 159:1148, 1955.
46. Coleman, M., and Siegal, B. B.: Studies in penicillin hypersensitivity. II. The significance of penicillin as a contaminant. J. Allergy, 26:253, 1955.
47. Combes, F. C., and Reisch, M.: A clinical evaluation of a piperidine compound alone and combined with calcium intravenously in antihistamine therapy. J. Invest. Dermat., 24:191, 1955.
48. Cornbleet, T.; Hoit, L.; and Sickley, J. F.: Fixed eruption. Arch. Dermat., 71:507, 1955.
49. Cortes, F. M., and Monteil, J.: Allergy to chicle; report of a case and review of the literature. Alergia, 3:41, 1955.
50. Costello, P. J.: Local treatment of dry contact-type dermatoses with antihistamine cream. Pennsylvania M. J., 58:201, 1955.
51. Council on Industrial Health. Dermatoses due to oils used in industry. J.A.M.A., 157:1611, 1955.
52. Council on Pharmacy and Chemistry. The present status of chlordane. J.A.M.A., 158:1364, 1955.
53. Crotty, R. Q.: Erythroderma desquamativum (Leiner's disease). Arch. Dermat., 71:587, 1955.
54. Cruz Hernandez, H., and Rosa-Febles, C. R.: Anaphylactoid shock due to penicillin. Bol. Asoc. méd. Puerto Rico, 47:323, 1955.
55. Davis, M. J., and Moursund, M. P.: Electrostatic electricity as possible factor in pruritus of dry skin dermatoses. Arch. Dermat., 71:224, 1955.
56. Denber, H. C. B.: Correspondence. Appraisal of drug reactions. J.A.M.A., 158:586, 1955.
57. Dogliotti, M.: Passive transfer of Prausnitz-Küstner method and gamma globulin. Minerva dermat., 29:388, 1955.
58. Dougherty, J. W.; Raisch, M.; and Lewis, G. M.: Lowered resistance to infection resulting from cortisone and corticotropin. New York State J. Med., 54:2964, 1954.

59. Downing, J. G.: Dermatologic therapy. New England J. Med., 253:184, 1955.
60. Downing, J. G.: Dermatologic therapy. New England J. Med., 253:234, 1955.
61. Dumm, J. F.; Raimondi, J.; and Moreno Ramirez, C.: Anaphylactic reaction caused by a mixture penicillin-streptomycin procaine. Alergia, 2:73, 1955.
62. Edge, J. R.; Fazlullah, S.; and Ward, J.: Hypersensitivity angiitis. Lancet, 1:1153, 1955.
63. Editorial. Besnier's prurigo. Brit. M. J., 2:1134, 1955.
64. Editorial. Hydrocortisone in anogenital pruritus. Brit. M. J., 2:896, 1955.
65. Eisenberg, B. C.: Contact dermatitis from selenium sulfide shampoo. Arch. Dermat., 72:71, 1955.
66. Epstein, S.: Hexachlorophene (G-11) in the treatment of eczematous dermatoses. Arch. Dermat., 71:692, 1955.
67. Esteves, J., and Brandão, N.: Lofflerscher Symptomenkomplex und medikamentose Hautuberempfindlichkeit. Hautarzt, 6:349, 1955.
68. Everall, J.; Truter, M. R.; and Truter, E. V.: Epidermal sensitivity to chromium, cobalt and nickel. Acta dermat.-venereol., 34:447, 1954.
69. Feldman, F. F., and Newman, B. A.: Eczema herpeticum (Kaposi's varicelliform eruption): report of three recurrent cases. Arch. Dermat., 71:399, 1955.
70. Ferrara, R. J., and Pinkus, H.: Alseroxylon in the treatment of pruritic and psychogenic dermatoses. Arch. Dermat., 72:23, 1955.
71. Finn, O. A.: Medical Memoranda. Long-term prognosis in infantile eczema. Brit. M. J., 1:772, 1955.
72. Fisher, R. S.; Freimuth, H. C.; O'Connor, K. A.; and Johns, V.: Boron absorption from borated talc. J.A.M.A., 157:503, 1955.
73. Fitzpatrick, T. B.; Griswold, H. C.; and Hicks, J. H.: Sodium retention and edema from percutaneous absorption of fludrocortisone acetate. J.A.M.A., 158:1149, 1955.
74. Fox, E. D.: Sulphonamide sensitivity. Lancet, 1:203, 1955.
75. Foxworthy, D. T.; Poske, R. M.; Barton, E. M.; Baker, L. A.; and Montgomery, M. M.: Adrenocorticotropin and cortisone in the treatment of severe Reiter's syndrome. Ann. Int. Med., 44:52, 1956.
76. Franceschini, G.: Incidenza della ipersensibilita clinica ai medicamenti negli asmatici bronchiali. Progr. méd., Paris, 11:431, 1955.
77. Frank, L., and Stritzler, C.: Prednisolone topically and systemically; a clinical evaluation in selected dermatosea: preliminary report. Arch. Dermat., 72:547, 1955.
78. Frank, L.; Stritzler, C.; and Kaufman, J.: Hydrocortisone (compound F) free alcohol and hydrocortisone acetate for topical use; a clinical evaluation. Arch. Dermat., 71:117, 1955.
79. Frankel, D. D., and Stutsman, R. E.: The prophylaxis of penicillin reactions with chlorprophenpyridamine maleate injection 100 mg. per cc. Ann. Allergy, 13:563, 1955.
80. Fromer, J. L.: Anaphylactoid drug reactions: recognition and management. Lahey Clin. Bull., 9:249, 1956.
81. Fromer, J. L.: Dermatologic concepts and management of pruritus ani. Am. J. Surg., 90:805, 1955.
82. Fromer, J. L.: Dermatologic allergy. Ann. Allergy, 13:720, 1955.
83. Fromer, J. L.: Urticaria (hives) and angioneurotic edema. In: Current Therapy. Philadelphia: W. B. Saunders Company, 1957 (in press).
84. Gardner, F. H., and Diamond, L. K.: Autoerythrocyte sensitization; form of purpura producing painful bruising following autosensitization to red blood cells in certain women. Blood, 10:675, 1955.
85. Gaté, J.; Coudert, J.; and Vayre, J.: Périartérite noueuse ulcérée actuellement guérie par la nivaquine avec sédation complète sous l'effet de ce traitement de toutes les manifestations douloureuses d'un très important rheumatisme déformant. Bull. Soc. franç. dermat. et syph., 2:174, 1955.
86. Gaul, L. E.: Comparison of patch and contact test responses in chromate sensitivity. Ann. Allergy, 13:243, 1955.
87. Gaul, L. E.: Drug eruptions from sulfonamides. Arch. Dermat., 71:740, 1955.
88. General News. Penicillin in milk. Arch. Dermat., 72:334, 1955.
89. Glaser, J.: Prophylaxis of allergic disease with special reference to the newborn infant. New York State J. Med., 55:2599, 1955.
90. Gleckler, W. J.: Hypercalcemia and renal insufficiency due to sarcoidosis: treatment with cortisone. Ann. Int. Med., 44:174, 1956.
91. Goldman, J. L.: Newer concepts in otolaryngological diagnosis and therapy. J.A.M.A., 157:30, 1955.

92. Goluboff, N., and MacFadyen, D. J.: Methemoglobinemia in an infant, associated with application of a tar-benzocaine ointment. J. Pediat., 47:222, 1955.
93. Goudy, J. M., and Masters, H. A.: Cortisone in black widow spider bite. J. Oklahoma M. A., 47:309, 1954.
94. Grater, W. C.: Intravenous hydrocortisone in allergy; preliminary report. Ann. Allergy, 13:191, 1955.
95. Groenewegen, J. T.: Sulfonamides in erythroderma medicamentosa. Hautarzt, 6:377, 1955.
96. Grolnick, M.: Sensitization of the human skin: a study of location of sites and of exposure time of excitant. J. Allergy, 26:542, 1955.
97. Guy, W. B., and Green, M.: Adjunctive therapy in dermatology with bacterial pyrogen (Piromen). Arch. Dermat., 72:420, 1955.
98. Haeberlin, J. B., Jr.: The general treatment of allergic dermatoses. Ann. Allergy, 13:571, 1955.
99. Hahn, H. J. A.: A case of Stevens-Johnson syndrome with extensive surgical emphysema. Brit. M. J., 1:1321, 1955.
100. Hansen, J. E., and Cleve, E. A.: Fatal hypersensitivity to PAS and streptomycin. Dis. of Chest, 28:577, 1955.
101. Haxthausen, H.: Some experiments with electrophoretic patch tests. J. Invest. Dermat., 24:211, 1955.
102. Haxthausen, H.: Generaliserede ids (autosensibilisering) ved varicøse eczemer. Ugesk. f. laeger, 117:1501, 1955.
103. Hill, L. W.: Hydrocortisone ointment in the treatment of infantile eczema. New England J. Med., 252:1038, 1955.
104. Hill, L. W.: Treatment of eczema in infants and children. J. Pediat., 47:141, 1955.
105. Hill, L. W.: Treatment of Eczema in Infants and Children. St. Louis: C. V. Mosby Co., 1956.
106. Hill, L. W.: Growth of 43 allergic children during cortisone administration. New England J. Med., 253:821, 1955.
107. Hodges, H. H., and Lazerte, G. D.: Jaundice and agranulocytosis with fatality following chlorpromazine therapy. J.A.M.A., 158:114, 1955.
108. Hollander, L.: Dermatitis caused by metal strands. Arch. Dermat., 71:735, 1955.
109. Hollander, L.: Angioneurotic edema caused by cigarette filter tip. Arch. Dermat., 72:468, 1955.
110. Hypnotism in dermatology. Dermatologists group discussion. Brit. M. J., 1:1214, 1955.
111. Ingram, J. T.: Besnier's prurigo: an ectodermal defect. Brit. J. Dermat., 67:43, 1955.
112. Ingram, J. T.; Brain, R. T.; Cruickshank, C. N. D.; Dowling, G. B.; Gell, P. G. H.; Goldsmith, W. N.; Long, D. A.; Percival, G. H.; and Hellier, F. F.: Treatment of skin disorders with A.C.T.H. and cortisone: first report of the Medical Research Council panel on dermatological applications of A.C.T.H. and cortisone. Brit. M. J., 2:1307, 1954.
113. Jadassohn, W.; Bujard, E.; and Brun, R.: Experimental eczema of guinea-pig nipple. J. Invest. Dermat., 24:247, 1955.
114. Jahrmarker, H.: Über Desensibilisierung bei Streptomycin-Allergie des Pflegepersonals. Ärztl. Wchnschr., 10:873, 1955.
115. Jambor, J. J., and Suskind, R. R.: Etiological appraisal of hand dermatitis. J. Invest. Dermat., 24:379, 1955.
116. Järnecke, H.: Silicon in der Prophylaxe und Therapie der Gewerbedermatosen. Deutsche med. Wchnschr., 80.755, 1955.
117. Jensen, B.: Schönlein-Henoch purpura; 3 cases with fish or penicillin as antigen. Acta med. Scandinav., 152:61, 1955.
118. Jillson, O. F., and Adami, M.: Allergic dermatitis produced by inhalant molds. Arch. Dermat., 72:411, 1955.
119. Jillson, O. F., and Piper, E. L.: Inhalant allergens in dermatitis: role in dermatitis of the hands. Arch. Dermat., 71:436, 1955.
120. Johnstone, D. E.; Basila, N.; and Glaser, J.: A study on boric acid absorption in infants from the use of baby powders. J. Pediat., 46:160, 1955.
121. Klüken, N.: Experimental findings with reference to the role of climatic effects on exudative eczematoid (Rost). Hautarzt, 6:220, 1955.
122. Kölbl, H., and Wolf, H. G.: Beitrag zur Pathogenese und Therapie der Kälteurtikaria. Allergie, Stuttg. In: Deutsche med. Wchnschr., 79:1833, 1954.
123. Kreidberg, M. B.; Dameshek, W.; and Latorraca, R.: Acute vascular (Schön-

lein-Henoch) purpura—an immunologic disease? New England J. Med., 253:1014, 1955.
124. Labelle, A., and Tislow, R.: Studies on prophenpyridamine (trimeton) and chlorprophenpyridamine (chlortrimeton). J. Pharmacol. and Exper. Therap., 113:72, 1955.
125. Lang, L. P., and Clagett, H., Jr.: Anaphylactic reaction following oral administration of penicillin. New England J. Med., 253:652, 1955.
126. Lapin, J. H.: The incidence of allergic reactions to penicillin in infants and children; further evidence collected during the course of penicillin prophylaxis. Ann. Allergy, 13:169, 1955.
127. Lapin, J. H., and Tuason, J.: Immunization adenitis. J.A.M.A., 158:472, 1955.
128. Laugier, P.: Cure de sommeil et dermatoses prurigineuses. Ann. dermat. et syph., 82:51, 1955.
129. Leese, W. L. B.: Prolonged treatment of Schönlein-Henoch syndrome with corticotrophin. Lancet, 2:851, 1955.
130. Leider, M.: The allergy of infection: statements, speculations and syntheses. J. Invest. Dermat., 24:255, 1955.
131. Levin, S. J.: Corticotropin and steroid hormone therapy of allergic states in children. Pediatrics, 16:416, 1955.
132. Lewis, G. N., and Sawicky, H. H.: Contact dermatitis from chlorpromazine. J.A.M.A., 157:909, 1955.
133. Lewis, I. C.: The Schönlein-Henoch syndrome (anaphylactoid purpura) compared with certain features of nephritis and rheumatism. Arch. Dis. Childhood, 30:212, 1955.
134. Librach, I. M.: Erythema multiforme bullosa (Stevens-Johnson syndrome); some observations on pathogenesis and on treatment with cortisone and ACTH. Postgrad. M. J., 31:570, 1955.
135. Livingood, C. S.; Hildebrand, J. F.; Key, J. S.; and Smith, R. W., Jr.: Studies on the percutaneous absorption of fludrocortisone. Arch. Dermat., 72:313, 1955.
136. Lovell, R. G.; Mathews, K. P.; and Sheldon, J. M.: Dermatitis venenata from tree pollen oils; a clinical report. J. Allergy, 26:408, 1955.
137. Lovell, R. R., and Rose, G. A.: Symptoms, diagnosis and treatment of polyarteritis. Postgrad. M. J., 31:382, 1955.
138. Lowell, F. C.: Allergic reactions to sulfonamide and antibiotic drugs. Ann. Int. Med., 43:333, 1955.
139. Lubowe, I. I.: Use of hydrocortisone and 9-alpha-fluorohydrocortisone derivatives; evaluation in the treatment of the pruritic dermatoses. Arch. Dermat., 72:164, 1955.
140. Lyell, A.: Reaction to cinnabar in a tattoo. Brit. J. Dermat., 67:313, 1955.
141. MacKenna, R. M.: The art of dermatology. Brit. M. J., 2:449, 1955.
142. Maffei, R., and Napolitano, L.: Reazioni allergiche alla penicillina nei lavoratori addetti alla produzione dell'antibiotico. Minerva med., 46:1785, 1955.
143. Mahrer, R. A., and Maret, R.: Agranulocytosis complicating PAS and streptomycin therapy. U. S. Armed Forces M. J., 6:1193, 1955.
144. Malkinson, F. D., and Ferguson, E. H.: Percutaneous absorption of hydrocortisone-4-C 14 in two human subjects. J. Invest. Dermat., 25:281, 1955.
145. Malkinson, F. D., and Wells, G. C.: Adrenal steroids in periarteritis nodosa. Arch. Dermat., 71:492, 1955.
146. Maloof, C. C.: Use of edathamil calcium in treatment of chrome ulcers of the skin. Arch. Indust. Health, 11:123, 1955.
147. Margolis, L. H.; Butler, R. N.; and Fischer, A.: Nonrecurring chlorpromazine dermatitis. Arch. Dermat., 72:72, 1955.
148. Marley, E.: Medical Memoranda. Non-thrombocytopenic purpura after administration of chlorpromazine hydrochloride. Brit. M. J., 2:1126, 1955.
149. Marsden, C. W., and Morgan, J. K.: Medical Memoranda. Sudden collapse in infantile eczema treated with cortisone. Brit. M. J., 2:659, 1955.
150. Massone, G.: Incidenti in corso di trattamento eparinico: reazioni di tipo allergico. Minerva ginec., 7:491, 1955.
151. Matheson, A., and Elegant, L.: Penicillin reactions in children; a study of the value of the skin test in penicillin sensitization. J. Allergy, 26:415, 1955.
152. Mathews, K. P.; Hemphill, F. M.; Lovell, R. G.; Forsythe, W. E.; and Sheldon, J. M.: A controlled study on the use of parenteral and oral antihistamines in preventing penicillin reactions. J. Allergy, 27:1, 1956.
153. Mauer, E. F.: The toxic effects of phenylbutazone (Butazolidin): review of the literature and report of the twenty-third death following its use. New England J. Med., 253:404, 1955.

154. Mayer, R. L.: Exposure as determining factor for type of sensitization. Internat. Arch. Allergy, 6:270, 1955.
155. Mayer, R. L.: Shortcomings of the experimental methods for detection of sensitizing properties of new drugs. J. Allergy, 26:133, 1955.
156. Mayer, R. L.; Eisman, P. C.; and Jaconia, D.: Experimental sensitization of guinea-pigs to 1-hydrazinophthalazine; with a discussion on the use of guinea-pigs for the forecast of clinical sensitizations. J. Invest. Dermat., 24:281, 1955.
157. Meara, R. H.: Skin reactions in atopic eczema. Brit. J. Dermat., 67:60, 1955.
158. Medico-Legal. Death from salicylate idiosyncrasy. Brit. M. J., 1:363, 1955.
159. Morris, G. E.: Chromate dermatitis from chrome glue and other aspects of the chrome problem. Arch. Industr. Health, 11:368, 1955.
160. Morrisset, L. M.: Penicillin anaphylaxis; case report. Texas J. Med., 51:77, 1955.
161. Mullins, J. F., and Shapiro, E. M.: Clinical evaluation of hydrocortisone ointment. GP, 12:59, 1955.
162. Murphy, J. C.: Chloroquinaldon (Sterosan) in dermatologic therapy. Rocky Mountain M. J., 52:530, 1955.
163. Nairn, R. C., and Anderson, T. E.: Erythrodermia with lipomelanic reticulum-cell hyperplasia of lymph nodes (dermatopathic lymphadenitis). Brit. J. M., 1:820, 1955.
164. Nexmand, P. H.: Exudative diffuse and papular dermatosis developed after discontinuation of ACTH and cortisone treatment of eczematous skin diseases. Danish M. Bull., 2:97, 1955.
165. Nørgaard, O.: Investigations with radioactive Ni_{65} into resorption of nickel through skin in normal and nickel hypersensitive persons. Acta dermat.-venereol., 35:111, 1955.
166. Nooijn, R. O.: Rehabilitation in industrial dermatoses. Arch. Dermat., 72:462, 1955.
167. O'Driscoll, B. J.: Desensitization of nurses allergic to penicillin; report of a case. Brit. M. J., 2:473, 1955.
168. O'Keefe, E. S.: Relationship between a careful dietary study and cortisone therapy in the treatment of infantile eczema. Ann. Allergy, 13:96, 1955.
169. O'Leary, P. A.: Discussion. Case for diagnosis: dermatomyositis? Arch. Dermat., 71:417, 1955.
170. Parsons, D. J.: Bedbug bite anaphylaxis misinterpreted as coronary occlusion. Ohio M. J., 51:669, 1955.
171. Pätiälä, R.; Kajas, S.; and Kalliola, H.: Irritation of the skin by synthetic detergent solutions; an experimental study. Ann. chir. et gynaec. Fenniae, Suppl. 5, 43:332, 1954.
172. Paton, M. D.; Riddell, M. J.; and Strong, J. A.: Aplastic anaemia following mepacrine treatment of lupus erythematosus. Lancet, 1:281, 1955.
173. Paull, A. M.: Occurrence of the "L. E." phenomenon in a patient with a severe penicillin reaction. New England J. Med., 252:128, 1955.
174. Pearson, J. R.; Binder, C. I.; and Neber, J.: Agranulocytosis following Diamox therapy. J.A.M.A., 157:339, 1955.
175. Pendergrass, E. P.; Hodes, P. J.; Tondreau, R. L.; Powell, C. C.; and Burdick, E. D.: Further consideration of deaths and unfavorable sequelae following the administration of contrast media in urography in the United States. Am. J. Roentgenol., 74:262, 1955.
176. Perlman, E.: Near fatal allergic reactions to bee and wasp stings: a review and report of seven cases. J. Mt. Sinai Hosp., 22:336, 1955.
177. Peters, G. A.; Henderson, L. L.; and Prickman, L. E.: Anaphylactic penicillin reactions: three nonfatal cases of reaction to oral penicillin with positive skin tests and one fatal case following intramuscular penicillin. Proc. Staff Meet., Mayo Clin., 30:634, 1955.
178. Pinkerton, J. R. H.: Correspondence. Agranulocytosis. Brit. M. J., 1:602, 1955.
179. Polák, L. Beitrag zum Problem der Pathogenese des Ekzems. Arch. klin. u. exper. Dermat., 201:124, 1955.
180. Porter, A. D.: Urticaria solaris. Brit. J. Dermat., 66:417, 1954.
181. Queries and Minor Notes. Antihistamines. J.A.M.A., 157:782, 1955.
182. Ibid. Aplastic anemia following drug therapy. J.A.M.A., 158:1482, 1955.
183. Ibid. Bullous lesions. J.A.M.A., 159:736, 1955.
184. Ibid. Dermatitis during pregnancy. J.A.M.A., 159:1700, 1955.
185. Ibid. Erythema multiforme. J.A.M.A., 159:1423, 1955.

186. Ibid. Fleeting erythematous patches and hives. J.A.M.A., 159:1255, 1955.
187. Ibid. Ink eradicator and dermatitis. J.A.M.A., 157:403, 1955.
188. Ibid. Occupational dermatitis. J.A.M.A., 159:154, 1955.
189. Ibid. Persistent urticaria following use of penicillin. J.A.M.A., 157:782, 1955.
190. Ibid. Poliomyelitis vaccine anl atopic dermatitis. J.A.M.A., 158:1406, 1955.
191. Ibid. Proposed theory for investigation of canker sores. J.A.M.A., 157:301, 1955.
192. Ibid. Reactions following vitamin B by vein. J.A.M.A., 157:302, 1955.
193. Ibid. Salk vaccine and penicillin sensitivity. J.A.M.A., 158:1406, 1955.
194. Ibid. Spider bites. J.A.M.A., 157:559, 1955.
195. Ibid. Urticaria in an infant. J.A.M.A., 157:875, 1955.
196. Ibid. Wetting agents in antibiotic mists. J.A.M.A., 157:1665, 1955.
197. Rajka, G.; Vincze, E.; and Csanyi, G.: Über Versuche zur Inaktivierung ekzematogener Stoffe in der Industrie. II. Dermatologica, 110:415, 1955.
198. Ramos e Silva, J.: L'innervation de la peau ne paraît jouer aucun rôle dans le mécanisme de la sensibilisation de la peau au dinitro-chlorobenzène; expériences sur des malades atteints de lèpre anesthésique. Dermatologica, 111:1, 1955.
199. Ramsay, A. G., and Jones, K. K.: The adsorption of soap on the skin. Brit. J. Dermat., 67:1, 1955.
200. Rasmussen, H.: Iodide hypersensitivity in the etiology of periarteritis nodosa. J. Allergy, 26:394, 1955.
201. Ratner, B., and Flynn, J. G.: Anaphylactogenic properties of piperazine citrate. Ann. Allergy, 13:176, 1955.
202. Rein, C. R., and Goodman, I. J.: Efficacy of reserpine (serpasil) and dermatological therapy. Arch. Dermat., 70:713, 1954.
203. Report of a special committee on use of epinephrine in connection with procaine in dental procedures. New York Heart Assn., Inc. J.A.M.A., 157:854, 1955.
204. Robinson, H. M., Jr.: Prednisone in treatment of selected dermatoses: preliminary report. J.A.M.A., 158:473, 1955.
205. Robinson, H. M., Jr.; Robinson, R. C., and Cohen, M. M.: Use of 9-alpha-fluorohydrocortisone in the therapy of dermatoses. Bull. School Med. Univ. Maryland, 40:72, 1955.
206. Robinson, R. C. V.: Use of fludrocortisone acetate in dermatoses. J.A.M.A., 157:1300, 1955.
207. Rockwell, E. M.: Study of several factors influencing contact irritation and sensitization. J. Invest. Dermat., 24:35, 1955.
208. Rodman, M. J.: A survey of potentially harmful household products. J. Pediat., 46:171, 1955.
209. Rodnan, G. P.; Black, R. L.; Bollet, A. J.; and Bunim, J. J.: Observations on the use of prednisone in patients with progressive systemic sclerosis (diffuse scleroderma). Ann. Int. Med., 44:16, 1956.
210. Rose, C., and Barron, J.: Anaphylactic shock as a complication of insulin coma therapy. Brit. M. J., 1:583, 1955.
211. Rose, G.: Hypersensitivity angiitis. Lancet, 1:1275, 1955.
212. Rosenthal, S. A.; Litt, J. Z. ;and Baer, R. L.: Failure to transfer allergic eczematous hypersensitivity from man to guinea pig. J. Invest. Dermat., 24:483, 1955.
213. Ross, I. P.: Intramuscular iron. Lancet, 1:51, 1955.
214. Rostenberg, A., Jr.: An anecdotal biographical history of poison ivy. Arch. Dermat., 72:438, 1955.
215. Rostenberg, A., Jr., and Best, W. R.: Studies in eczematous sensitizations. V. Role of regional lymph node. Arch. Dermat., 72:221, 1955.
216. Russell, B., and Last, S. L.: Besnier's prurigo: observations on abnormal cutaneous and central nervous reactions. Brit. J. Dermat., 67:65, 1955.
217. Russell, B., and Thorne, N. A.: Skin reactions beneath adhesive plasters. Lancet, 1:67, 1955.
218. Russell, B.; Pegum, J. S.; Thorne, N. A.; and Grange, R. V.: A valuation of hydrocortisone ointment. Lancet, 1:1038, 1955.
219. Salles-Gomes, L. F.; Bassoi, O. N.; and Patricio, L. D.: Eczema vaccinatum with vaccinial lesions strictly confined to the eczematous patches. Lancet, 2:1275, 1955.
220. Salomon, A.; Appel, B.; Dougherty, E. F.; Herschfus, J. A.; and Segal, M. S.: Scleroderma; pulmonary and skin studies before and after treatment with corticosone. Arch. Int. Med., 95:103, 1955.

221. Samitz, M. H.: Some dermatologic aspects of the chromate problem. Arch. Industr. Health, 11:361, 1955.
222. Sanchez, G.: Correspondence. In reply to "A defense of sodium dehydrocholate." New England J. Med., 252:552, 1955.
223. Santyan y Velasco, S., and Amore, F.: Terapia tissulare nella dermatite seborroide e nell'eczema del lattante. Clin. Pediat., 37:501, 1955.
224. Savitt, L. E.: Contact dermatitis encountered in the production of epoxy resins. Arch. Dermat., 71:212, 1955.
225. Schnitzer, A.: Die Bedeutung endogener Faktoren in der Pathogenese und im Verlauf des Ekzems. Dermatologica, 110:332, 1955.
226. Service, W. C.: Pentothal. Letters Internat. Corres. Club Allergists, 18:6, 1955.
227. Shaw, J. M., and Crowe, F. W.: Skin-protective ointments; comparative study including new silicone preparations. Arch. Dermat., 71:379, 1955.
228. Sheard, C., Jr.: Contact dermatitis from platinum and related metals. Arch. Dermat., 71:357, 1955.
229. Shelley, W. B., and Arthur, R. P.: Studies on cowhage (Mucuna pruriens) and its pruritogenic proteinase, mucunain. Arch. Dermat., 72:399, 1955.
230. Shmushkovich, J., and Davis, E.: Thrombocytopenic skin purpura following treatment with trinitrin. Brit. J. Dermat., 67:299, 1955.
231. Sidi, E.; Hincky, M.; and Gervais, A.: Allergic sensitization and photosensitization to Phenergan cream. J. Invest. Dermat., 24:345, 1955.
232. Siegal, S.: Correspondence. Skin testing for penicillin sensitivity. J.A.M.A., 159:1401, 1955.
233. Siegal, S.: The penicillin content of poliomyelitis vaccine (Salk) and its administration to allergic patients. Am. J. Pub. Health, 45:791, 1955.
234. Simons, R. D.: The effect of non-medicamentous enclosure and dermatologic rest on eczema. J. Invest. Dermat., 25:365, 1955.
235. Smith, C. C.: Urinary excretion of 17-ketosteroids and 17-hydrocorticosteroids after inunction of hydrocortisone ointment: attempts to demonstrate systemic absorption from topically applied hydrocortisone ointment. J. Invest. Dermat., 25:67, 1955.
236. Sneddon, I. B.: Berylliosis: a case report. Brit. M. J., 1:1448, 1955.
237. Spier, H. W., and Sixt, I.: Dependence of the results of patch tests in eczema on thickness of the stratum corneum. Hautarzt, 6:152, 1955.
238. Spring, M.: Swelling of interphalangeal joints as manifestation of drug allergy. Ann. Allergy, 13:160, 1955.
239. Steinberg, C. L., and Roodenburg, A. I.: Metacortandracin (Meticorten) in the treatment of disseminated lupus erythematosus and periarteritis nodosa. Ann. Int. Med., 44:316, 1956.
240. Steinhardt, M. J.: Urticaria and angioedema; statistical survey of 500 cases. Ann. Allergy, 12:659, 1954.
241. Storck, H.: Ekzem durch Inhalation. Schweiz. med. Wchnschr., 85:608, 1955.
242. Storck, H.: Index thrombopénique dans les états allergiques. Semaine d. hôp. Paris, 31:1897, 1955.
243. Storck, H.; Hoigné, R.; and Grossman, W.: New test for allergens. In: Migraine and vascular allergy. International Symposium in Basle. Brit. M. J., 2:320, 1955.
244. Strauch, J. H.: Erythema multiforme reaction following Salk vaccine. Bull. Assn. Mil. Dermat., 4:3, 1955.
245. Stritzler, C., and Frank, L.: Topical hydrocortisone-oxytetracycline therapy. Arch. Dermat., 71:736, 1955.
246. Stüttgen, G.: Zur Entstehung bullös-vesiculöser hämorrhagischer Exantheme in der Haut. Arch. klin. u. exper. Dermat., 201:311, 1955.
247. Szymanski, F. J.: Allergic vasculitis. Ann. Allergy, 13:408, 1955.
248. Tasker, J. R.: Fatal agranulocytosis during treatment with chlorpromazine. Brit. M. J., 1:950, 1955.
249. Thurmon, F. M.; Ottenstein, B.; and Bessman, M. J.: Chemical and biological tests with the toxic substance of poison ivy (urushiol) and its absorption by amberlite ion exchange resins. J. Invest. Dermat., 25:9, 1955.
250. Tilley, R. F., and Barry, H., Jr.: Chlorpromazine treatment for relief of itching in severe refractory neurodermatitis. New England J. Med., 252:229, 1955.
251. Tuft, L.: Inhalant allergens in management of atopic dermatitis. Am. J. Dis. Child., 89:210, 1955.
252. Tuft, L., and Heck, V. M.: Studies in sensitization as applied to skin testing procedures. II. Influence of allergen contact. J. Allergy, 26:59, 1955.

253. Tuft, L.; Ettelson, L. N.; and Schwartz, H.: Allergy to foods containing sulfuramino-acids, especially methionine; case report and clinical study. Am. J. M. Sc., 229:26, 1955.
254. Tuft, L.; Gregory, D. C.; and Gregory, J.: Evaluation of skin testing methods employed in diagnosis of penicillin allergy. Am. J. M. Sc., 230:370, 1955.
255. Turell, R.: Hydrocortisone therapy in control of anogenital pruritus. J.A.M.A., 158:173, 1955.
256. Ungar, J.: Enhancement of the antigenic activity of toxoids by sympathomimetic drugs. Brit. M. J., 2:20, 1955.
257. Van der Meiren, L., and Achten, G.: Etude clinique et histologique de l'urticaire bulleuse. Ann. dermat. et syph., 82:267, 1955.
258. Vowles, M.; Warin, R. P.; and Apley, J.: Infantile eczema: observations on natural history and prognosis. Brit. J. Dermat., 67:53, 1955.
259. Waldbott, G. E.: Fluorein. Letters Internat. Corres. Club Allergists, 18:1, 1955.
260. Weber, R. G.; Roth, G. M.; and Kierland, R. R.: Further contributions of vascular physiology of atopic dermatitis. J. Invest. Dermat., 24:19, 1955.
261. Weinstein, L.: The complications of antibiotic therapy. Bull. New York Acad. Med., 31:500, 1955.
262. Welsh, A. L.: Crossed fixed drug eruption from three antibiotics. Arch. Dermat., 71:521, 1955.
263. Wilson, H. T.: Standard patch tests in eczema and dermatitis. Brit. J. Dermat., 67:291, 1955.
264. Witten, V. H.; Shapiro, A. J.; and Silber, R. H.: Attempts to demonstrate absorption of hydrocortisone by a new chemical test following inunction into human skin. Proc. Soc. Exper. Biol. & Med., 88:419, 1955.
265. Witten, V. H.; Sulzberger, M. B.; Zimmerman, E. H.; and Shapiro, A. J.: A therapeutic assay of topically applied 9-α-fluorohydrocortisone acetate in selected dermatoses. J. Invest. Dermat., 24:1, 1955.
266. Woodhead, B.: The eczema-asthma syndrome: psychiatric considerations. Brit. J. Dermat., 67:50, 1955.
267. Wright, D. C.: Correspondence. Anaphylaxis after procaine penicillin. Brit. M.. J., 1:724, 1955.
268. Wright, E. T.; Graham, J. H.; Newcomer, V. D.; and Sternberg, T. H.: Evaluation of 9-α-fluorohydrocortisone acetate in treatment of various inflammatory dermatoses. Arch. Dermat., 72:69, 1955.
269. Year Book of Dermatology and Syphilology. Chicago: Year Book Publishers, Inc., 1955-1956.
270. Zion, M. M.; Goldberg, B.; and Suzman, M. M.: Corticotrophin and cortisone in the treatment of scleroderma. Quart. J. Med., 24:215, 1955.

OCCUPATIONAL ALLERGY

A course, organized by the Institute of Preventive Health, the Netherlands Society of Occupational Medicine, and the Netherlands Society of Allergy, will be held May 1 to 15, 1958, at The Hague, Netherlands.

The program covers allergy and allergic symptoms, allergic examination, and occupational allergy (bulbs and flowers, tomatoes and vegetables, bakery, chemical industry, tobacco-industry, wool and textile industry, farms and veterinarians, doctors, nurses and chemists, cement, turpentine, pharmaceutical industry, cosmetics, printers, house and mines.) Also discussed will be anti-allergic therapy and preventive measures. The planning committee includes Prof. Dr. H. A. E. van Dishoech, Leyden, Chairman; Prof. Dr. J. R. Prakken, Amsterdam; and Dr. D. A. Williams, Cardiff, Wales. Questions should be addressed to the Secretary, Dr. W. J. Quarles van Ufford, Emmallaan 17, Utrecht. The number of participants is restricted.

During each afternoon, excursions will be made to bulb farms, tomato nurseries, farms, hospitals, cigar factories, bakeries, pharmaceutical and chemical works, textile factories (including nylon and food processing plants) and other sources of occupational allergy.

Editorials

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

SEROTONIN, MENTAL DISTURBANCES AND ALLERGY

Further Implications

The demonstration by Dr. Mary Fink of the University of Colorado that serotonin induces anaphylactic shock in the egg-sensitive guinea pig merits special consideration for its implications in the field of allergy. In its anaphylactic action, as measured by its reaction in the sensitized uterine horn, serotonin appears to be 1,000 more times potent than histamine. But, significantly, this reaction is invariably and completely prevented by the prior addition to the bath of either reserpine or lysergic acid diethylamide (LSD).

The fact that both of these drugs have psychic effects—reserpine as a tranquilizer in disturbed states, and LSD as a cause of a schizophrenic-like syndrome—presents the allergist with an interesting and provocative set of new relationships.

If serotonin is—biologically and/or chemically—a key substance in both anaphylactic and psychic disorders, do these have some basic common relationship at the cell enzyme level? Apparently, at this level the mere presence of serotonin, depending on the prior condition of the cell, including its sensitization, may cause neither anaphylaxis nor allergy. Apparently in the same patient, at least, it does not invariably cause both.

What remains to be explored now is whether at this cell enzyme level some serotonin-related deviation from the "normal" processes can be a cause—primary or contributing—of either allergy or mental disorder. If so, are these causal mechanisms discrete or related?

TUBERCULOSIS CASE-FINDING

The annual report of the National Tuberculosis Association cites the fact that each year in this country 80,000 new cases of tuberculosis are reported. There are 16,000 annual deaths from tuberculosis. It is estimated that there are 800,000 who are actively diseased, of whom 250,000 are not under treatment. The total of active and inactive tuberculosis patients is estimated at 1,200,000.

The allergist who treats asthmatic patients is in an ideal situation for case-finding. If, added to the present preventive measures, every patient presenting any lung disorder were given the benefit of a roentgenogram, both tuberculosis (and carcinoma) of the lung would be discovered earlier.

In these days of steroid hormone therapy, routine studies are not only indicated before treatment but at intervals thereafter.

Let it not be said that anyone was "cured" of his allergy and subsequently presented himself for the treatment of a much more disabling and truly miserable disorder like tuberculosis.

ALLERGIC CELL RESPONSE

At the Third European Congress of Allergology, R. J. S. McDowall, who is Professor of Physiology of King's College of the University of London, asked and attempted to answer these three questions.

In the allergic patient, is it that an abnormal amount of histamine is liberated or, if histamine is present in normal amounts, is the allergic patient less capable than is the nonallergic subject of inactivating it? Or, thirdly, are the tissue cells generally or locally of the allergic patient more than normally sensitive to histamine?

If the third hypothesis be true, then there may be a partial explanation both for the variety of allergic phenomena and a relationship also to psychogenic factors.

What is the evidence? Bronchi are sensitive to minute amounts of sodium and potassium. Epinephrine which relaxes the bronchi increases blood potassium. Unfortunately for the elegance of the hypothesis, it also stimulates the pituitary and the adrenals, and, also, injected potassium salts are removed from the circulation by all tissue cells within a matter of minutes. Tests for sodium metabolism are associated with emesis which makes such experiments impractical.

But, if tissue cells are exposed to large amounts of histamine, they subsequently become sensitive to both sodium and potassium and as well to thermal stimuli. In blood plasma there is a ten-fold greater concentration of sodium and a one-tenth concentration of potassium as compared to tissue cells. If, in the allergic state, tissue sodium is low and tissue potassium is high, excitability may be correspondingly increased as it is decreased when sodium is high and potassium is low.

Hughes, working in McDowall's laboratory has shown that although blood sodium levels remain remarkably constant, nevertheless, in sensitized animals there is an increased and opposite permeability of tissue cells for sodium or potassium, the tissues showing themselves as unable to retain sodium as do nonsensitized controls.

Tissues inflamed or damaged by toxins of whatever source would have been damaged by histamine, particularly, and susceptible to such reactions, which, if shared by the adrenals making them also incapable of maintaining sodium equilibrium, would, if true help test this hypothesis.

As others have shown, the effects of such ionic imbalances on enzymatic processes can, in their way, alter the immunologic responses of cells.

Step by step, the picture as to what may be happening within the cells of our allergic patients becomes less and less foggy. Far-flung studies in many disciplines may yet be unified into a single comprehensive hypothesis.

Papers of Interest

Friebel, H., and Reichle, C.: Experimental animals and test results in the evaluation of analgesics and antitussives. Arch. exper. Path. Pharmakol., 229:400 1956.
For analgesics, mice and rats are better test animals and for antitussives, guinea pigs. Sixteen preparations were tested.

Friedman, H. T., and Marmelzet, W. L.: Adverse reactions to meprobamate. J.A.M.A., 162:628 (Oct. 13) 1956.
The administration of meprobamate is said to have caused three cases of paradoxical excitement, one of intestinal hyperperistalsis, one of palsy and five of skin responses.

Welsh, A. L., and Ede, M.: Observation on Pantho-F ointment. Ohio State M. J., 52:1052 (Oct.) 1956.
Of 170 patients treated with a combination of pantothenylol and hydrocortisone free alcohol, 113 responded well and fifteen poorly, with the remainder fairly well. Comparison is made with hydrocortisone. Of these patients, 156 had previously used topical hydrocortisone alone. Response to Pantho-F was equal in 102 of them, superior in forty-seven, and inferior in seven.

Stubenrauch, G. O.; Dalton, J. E.; Armstrong, B.; and Stares, H.: Clinical evaluation of therapeutic effects of a combined antibiotic ointment in pyodermas. J. Indiana M. A., 49:1063 (Sept.) 1956.
An antibiotic ointment, containing bacitracin, neomycin sulfate, polymyxin B, and benzalkonium chloride, was used on 167 patients. No contact dermatitis was noted.

Ross, S.: Penicillin: applied pharmacology. Clin. Proc. Children's Hosp. 12:149 (July) 1956.
Good review.

Horbaczewski, J.: Agranulocytosis associated with chlorpromazine therapy. Canad. M. A. J., 75:413 (Sept. 1) 1956.
In the Saskatchewan Hospital chlorpromazine is said to have caused a granulocytosis in one of 300 patients. Data not satisfactory.

Brockbank, W.; Brebner, H.; and Pengelly, C. D. R.: Chronic asthma treated with aerosol hydrocortisone. Lancet, 2:807 (Oct. 20) 1956.
No effect.

Hutner, L.: Oxytetracycline-hydrocortisone ointment (Terra-Cortril) in common dermatoses. Antibiotic Med. & Clin. Therap., 3:326 (Oct.) 1956.
Useful in dermatitides accompanied by bacterial invasion.

Riley, H. D., and Worley, L.: Salicylate intoxication. Pediatrics, 18:578 (Oct.) 1956.
Discusses pharmacology, pathogenesis, physiology, clinical effects and therapy in forty-two children.

Konzett, H.: The effects of 5-hydroxytryptamine and its antagonists on tidal air. Brit. J. Pharm., 11:289 (Sept.) 1956.
In cats and guinea pigs tidal air is reduced perhaps by bronchoconstriction, but antagonism is specifically noted by use of d-lysergic acid and bromo-LSD. May be discovery of great importance.

Chaudhry, N. C., and Saunders, L.: Sustained release of drugs from ion exchange resins. Pharm. J., 177:268 (Sept. 29) 1956.
With sulphonic acid cation exchange resins as vehicles sustained-release of oral ephedrine preparation may be accomplished.

Vollmer, H.: Topical use of fludrocortisone acetate in allergic dermatitis. A.M.A. Arch. Dermat., 74:300 (Sept.) 1956.
In controlled study with one side of the body treated, five of thirty-one patients were impoved, sixteen responded equally on both sides and ten were unimproved.

Christianson, H. B., and Perry, H. L.: Reactions to choral hydrate. A.M.A. Arch. Dermat., 74:232 (Sept.) 1956.
Report of seven patients who reacted cutaneously to chloral hydrate administration.

Cahn, M. M., and Einstein, J. Albert: The use of tranquilizing drugs in dermatology. Review and side reactions. Med. Center, 4:161 (Sept.) 1956.
Concludes that chlorpromazine, meprobamate and Rauwolfia may be helpful in patients in whom "nervous influences" are important.

Jawetz, E.: Antimicrobial chemotherapy. Ann. Rev. Microbiol., 10:85-114, 1956.
In 1954 the production of antibiotic agents totalled 920 tons. It is estimated that 5 to 10 per cent was prescribed properly.

Singleton, A. O., Jr., and Little, H. M.: The use of an antihistamine agent in preventing serum reactions following the injection of tetanus antitoxin. Surgery, 40:784 (Oct.) 1956.
Phenergan evidently does not lessen the incidence of reactions to tetanus antitoxin serum.

News Items

UNIFORM CHEMICAL LABELING LAW PROPOSED

The American Medical Association's Board of Trustees has authorized a first step toward protecting the public from potentially dangerous household and commercial chemicals.

The Board authorized the AMA committee on toxicology to draft a recommended "model" law on labeling of many possibly harmful chemicals not now regulated.

It would serve as a guide for writing regulations which would require labels to show such information as the product's contents, its possible dangers, directions for safe use, and first aid instructions.

Products involved include auto care and repair materials, paints and paint removers, putty, soldering fluids, household cleansers and polishers, heating and cooking fuels, laundering items, art supplies, and toys containing chemicals.

The law should be an "enabling act" under which later regulations could spell out necessary details for enforcement and compliance, according to Dr. Torald Sollmann, Cleveland, committee chairman.

The AMA committee plans to consult other organizations and individuals who are interested in the problem. These include the American Academy of Pediatrics, American Public Health Association, American Pharmaceutical Association, National Safety Council, leading trade associations, and various state and national government regulatory agencies.

HYDROCORTISONE AND HYDROCORTISONE ACETATE OINTMENTS AND LOTIONS DENIED EXEMPTION FROM PRESCRIPTION-DISPENSING REQUIREMENTS

In the *Federal Register,* January 17, 1957, are published the results of the public hearing held August 15-17, 1956. Ten pharmaceutical firms had petitioned the Food and Drug Administration to exempt hydrocortisone and hydrocortisone acetate ointments and lotions from the prescription-dispensing requirement. A proposed order to this effect was published in the *Federal Register,* January 20, 1956. It was challenged by members of the medical and pharmaceutical professions, and the public hearing mentioned above was called.

Based on testimony from dermatologists, the Food and Drug Administration reversed its proposed decision and has published an order denying proposals to permit sale without prescription of ointments and lotions containing hydrocortisone and hydrocortisone acetate. According to the Commissioner's statement, the available evidence failed to show that these drugs were safe for use without medical supervision.

The evidence opposing the proposed exemptions indicated that there were (a) studies demonstrating absorption of varying amounts of hydrocortisone through the skin and mucous membranes adjoining skin areas; (b) insufficient evidence to establish conclusively whether the amount absorbed might cause clinically significant systemic effects; (c) documented cases of adverse effects where the application of such preparations caused a spread of infection; (d) the belief of qualified experts that laymen in general cannot differentiate between skin conditions in which the ointments or lotions are indicated and those in which they are contraindicated; (e) the belief of well qualified experts that it is impossible to write adequate directions for the use of these ointments or lotions in self-medication; (f) the opinion of well qualified experts that the temporary relief and the absence of cure from

the use of these ointments would not be within the scope and knowledge of the non-medical consumer; and (g) the difference of opinion among well qualified medical experts whether the ointments or lotions are safe and useful for self-medication.

The Commissioner, George P. Larrick, is to be congratulated on having taken a stand which protects the public against the indiscriminate use of the steroid hormones in ointment and lotion forms.

IN MEMORIAM

J. R. BRUCE

"Bob" Bruce, as he was known by his legion of friends, died recently at the age of eighty-one. He was founder and chairman of the board of Bruce Publishing Company, St. Paul, publishers of the ANNALS OF ALLERGY. Born in Freedom, Kentucky, Mr. Bruce moved to St. Paul in 1903 where he has resided ever since. The Bruce Publishing Company produces not only its own journals but those of many other publishers as well. Mr. Bruce was a friend of physicians and was particularly interested in medical publications—*Minnesota Medicine, The Journal of the Michigan State Medical Society*, the ANNALS OF ALLERGY, and other medical journals are published by his company.

I have known "Bob" personally for many years. When the College was founded, Mr. Bruce made an unprecedented offer to publish the ANNALS OF ALLERGY which has never been equalled since. He offered to print the magazine without any loss to the College the first year, and to share equally any profits as they accrued thereafter. Through the years we had many lunches together, planning and discussing the operation of the ANNALS. His suggestions were always unselfish and always for the good of the College, of which he was very fond. He had an inquisitive mind and a keen business sense, as well as a charming sense of humor. Up until his last illness he had a cheerful sparkle in his eye and a gift for making one's worries lighter.

Mr. Bruce took a prominent part in business and civic associations. He was a member of Zuhrah Shrine and of the Town and Country Club. He is survived by his wife, Anna H. Bruce, a son, J. R. Bruce, Jr., who succeeds his father in active participation in the company, a daughter, Mrs. W. G. Shepherd, and six grandchildren.

College members, particularly the Editorial Board of the ANNALS, keenly regret Mr. Bruce's departure and extend their sincere sympathy to his family.

F. W. WITTICH, M.D.

BOOK REVIEWS

FUNDAMENTALS OF IMMUNOLOGY. William C. Boyd, Professor of Immunochemistry, Boston University School of Medicine, Boston, Massachusetts. Third edition. 775 pages, including index. 1956. Price $10.00.

Those of us who qualified many years ago remember much of what we have learned as modified by our clinical and research experiences and the subsequent reading of papers as by chance we meet them in the journals. We often possess the past elementary and the present advanced knowledge and frequently lack what lies between. There is no better method of filling this lacuna than the rereading of a text with which we were once familiar.

The reviewer has read each of the three editions of "Boyd" each time with interest and profit. The author has not hesitated to reverse himself as new knowledge in the field necessitated changes in attitudes. He has amplified the sections devoted to the clinical aspects of immunology. He has modernized and expanded the section on statistical methods. Although the introduction states that the book is not a comprehensive review, there are few, if any, fundamental studies to which reference is not made.

The author also explains that, although it represented more work for him the bibliography (as in the ANNALS), is arranged alphabetically by authors, and *ibids, loc. cits* and other mystic symbols have been avoided.

Of interest to the allergist who recognizes the need of basic knowledge are the chapters dealing with immunity and immunology, antibodies and antibody specificity, antigens, cell antigens, antibody-antigen reactions, immediate and delayed hypersensitivity and the practical use of immunity and hypersensitivity. Fifty pages are given to blood groups, twenty-five to complement and twenty to auto-immunization. On the other hand, the more than 100 pages devoted to laboratory and clinical techniques should be read by every practicing allergist.

The book has satisfied and will continue to be read with satisfaction by students and practicing physicians and research workers.

PROCEEDINGS OF THE FIRST INTERNATIONAL CONFERENCE ON THE CLINICAL AND METABOLIC EFFECTS OF METICORTEN (PREDNISONE) AND METICORTELONE (PREDNISOLONE). Gladys S. Koch, A.B., Editor. New York: Georgian Press, 1956. 309 pages, no index.

As is now generally known, a team of steroid chemists and biologists, consisting of William Charney, Emanuel B. Hershberg, Hershel L. Herzog, Arthur Nobile, Preston L. Perlman and Sibylle Tolksdorf, working in the research laboratories of the Schering Corporation, discovered prednisone and prednisolone. The studies of these compounds were initiated in the National Institutes of Health. They were then released for clinical investigation by research workers in all of the fields in which steroid hormones had previously been proven to be useful. Of these, thirty-six were invited to participate in the First International Conference to communicate their findings rapidly to each other and to an audience of interested physicians. The papers, edited by Gladys S. Koch, have been gathered together in this volume.

The results of the treatment of allergic disorders can be evaluated from papers presented by Alvan L. Barach, John M. Sheldon, Ethan Allan Brown, Bram Rose, and their associates. Representing the dermatologists are George C. Andrews, Charles R. Rein, Harry M. Robinson, Jr., Carl T. Nelson, their colleagues and others.

Thomas D. Stevenson discusses the effects of the drugs on blood dyscrasias. Clinical and metabolic studies are reported upon by Laurance W. Kinsell and his colleagues. Edward W. Boland, President, American Rheumatism Association, discusses his experiences with modified steroid hormones in rheumatoid arthritis.

Relationships to physiology, metabolic and hormonal and nutritional balances are discussed.

Although some minor portions of the book have been modified by subsequent experience, it is remarkable that the early investigators did such sound and solid work and so little of their data are dated. Anyone working with the newer steroid hormones should be familiar with this basic material.

RELAZIONI E COMUNICAZIONI. The Proceedings of the Third European Congress of Allergology. Edited by Drs. Antonio Lunedei and Umberto Serafini. 575 pages including index. Rome, Italy: Il Pensiero Scientifico, 1956. Price 7500 Lire.

The present volume represents the transactions of the Third European Congress of Allergology held at Florence, Italy, September 12-15, 1956. It is the first of two volumes. The official languages were Italian, French, English and German. For those who may not be able to read one or another of these languages, some of the papers, besides those printed in English, are well worth the translation.

This book is reviewed at length and in some detail because it embodies the virtues and the faults of international congresses. For just so long as they serve both to disseminate knowledge and to furnish the means of a tax-deductible holiday, they will include the good and the bad, the basic and the unbelievable in science. For the sections, workers of known repute are invited. For the general session, anyone who wishes to present a paper may submit one. No one may have listened, but the presentation acquires the dignity of program listing and the implied approval of appearing in print.

In many aspects of science, other than medicine in general, and in allergy in particular, Europe has furnished the hypotheses and the Americas their practical applications. The excellent papers of this Congress again accent this observation.

The factors that influence the local fixation of antibodies in the tissues is discussed in separate papers by Pasteur Vallery-Radot and his colleagues of Paris, (in French), by Melli of Milan (in Italian), and by van Dishoeck of Leyden (in English). The distribution of atopic reagins in serum protein fractions is reviewed by Colldahl of Stockholm (in English), and cellular antibodies by Schmidt of Freiburg (in German). Other papers and sixteen abstracts round out the other aspects of this ever interesting problem.

The second section of the Proceedings deals with allergy of the neuro-vegetative system with papers by Werner (in German), by Farrerons-Co. (in English), by McDowall (in English), by Panzani et al and by Halpern, Charpy and by Bovet et al (all four in French). Here again other papers and abstracts help to complete the picture.

The third section is concerned with present-day knowledge of the factors that augment allergic states. In the first paper of this group entitled "Alimentary Factors Increasing Allergic Conditions," Surinyach of Barcelona (in English) states bluntly that according to his experience, the leukopenic test of Vaughan, the eosinophilia test of Randolph, the pulse lability test of Coca and the cholesterinemia test of Laborie are all inaccurate in mild food allergy and useless in severe cases. He is equally discouraged with skin tests in general in food allergy. Surinyach's experiments with causing hemolysis in cases of favism *by inhalation* of the powdered

beans will be recalled. He feels that because of urbanism and other factors, such as canning and preservation of foods, alimentary allergy is decreasing.

The paper which follows by Spoujitch et al (in French) has as its thesis the increase in food allergy as seen to be present as 23 per cent in urban and only 3 per cent in a nonurban group. On the other hand, Sangiorgi (in Italian) feels that allergy of all types is on the increase due to the "frantic rhythm of modern life." All of the authors listed in this section agree that allergy of every type is probably on the increase, although the reasons given differ.

The fourth section is devoted to the "Mechanisms of Delayed Reactions." Excellent papers in English by Bruun, by Pepys, and by Sulman make good reading.

The fifth section is concerned with the "Standardization of Allergenic Extracts." Here the paper by Augustin (in English) on methods of standardizing extracts and their limitations should be available to every practicing allergist. It is stated that the Ouchterlony technique will "revolutionize and fertilize immunology almost as much as paper chromatography has revolutionized the chemistry of proteins." This section is worth the price of the book.

The sixth section, "Allergological Classification and Terminology," is disappointing. The seventh with ninety "free subjects" is depressing. The contributions vary from excellent to poor. For this no one is responsible except the physicians themselves who, presented with an opportunity to mount the podium, cannot be restricted or restrained. And, unfortunately, given the present pattern of international congresses nothing can be done.

The second volume will contain the texts of the introductions to each section, the discussion of the papers, and the closing remarks.

THE PATIENT SPEAKS. Harold A. Abramson. 237 pages. No index. Bibliography. Vantage Press, 1956. Price $3.50.

After reading many books which deal with patients in numbers, it is refreshing to review one concerned with one patient studied "in depth."

In "The Patient Speaks," Dr. Abramson gives us selected verbatim material of a female patient who came to him suffering from eczema, hay fever and asthma. On her side, she is as unrestrained as she is articulate and intelligent. On his side, with admirable restraint, he nowhere states that the three disorders were caused by psychologic difficulties, but rather limits himself to comments on the significance of some of the patient's outbursts. He leaves the door open for an interpretation that the disorders were originally atopic, and may have been perpetuated, long after their original causes ceased to operate, by the psychogenic factors described. Presented to the reader are the patient's spontaneous conversations, interspersed with occasional questions by the physician and his notes as to the significance of the material.

It is obvious that the conflicts between the patient and her mother have existed during the period of study. When the relationship intermittently deteriorates, the patient itches and scratches. The recordings report, as well, her reactions toward her eczema, hay fever and asthma, as they relate to limitations of activity, choice of friends, neighbors, dates and her husband.

The book may, at first glance, appear to present a case of special pleading for the existence of the "Cronus Complex," but its significance is much greater. As the reader follows the patient's (and the physician's) stream of consciousness, he will find himself participating on two levels, first reading, and second, dredging up those of his own memories which although he thinks they are unique and personal, are truly part of universal interpersonal adjustments.

Many parts of these verbatim reports are worthy of verbatim quotation. The reviewer was forced to restrain himself in his choices of quotable "quotes." His

comments upon them would have required another book. The following were rigorously selected.

Page XI: How can psychiatry reasonably present what happens during the course of psychoanalysis to the reader who is not being psychoanalyzed? How can communication occur without causing serious anxiety due to exposure of the reader to his own deeper tensions? . . . The practical elimination of technical procedures and of professional terminology . . . (will lead to its being) easily read and sensitively understood. . . .

Page XIV: But this link (maternal rejection) so strongly exploited by the exponents of the maternal-rejection idea does not give the total picture of the complexity of the emotional tensions between Alice and her mother. . . . From the Preface by M. Murray Peshkin, M.D.

Page 35:—
Alice: I say to her (her mother) "I can't explain it to you. I can't tell you."
Doctor's Comment: "There is always a vested interest of close relatives of a patient in analysis to preserve the family balance of power."
Reviewer: How true! How often unconsidered!

Page 36:—The patient recalls having lied, sticking to her lies and attempting suicide.
Reviewer: Telling untruths to oneself is probably the greatest common cause of neurosis. The universe will not change to protect the liar. The amount of displaced energy used to maintain and protect a lie is prodigious. Before the truth is out the liar suffers from a floating anxiety and afterwards from a sense of guilt. The habitual liar is punished by the fact that when he tells the truth he appears to be telling lies.

Page 39:—
Alice: Her idea is that unless she shows interest by asking questions she is not concerned about me.
Doctor's Comment: This is the development of the struggle for independence to come.
Reviewer: In interpersonal relationships, questions, when not instruments for obtaining knowledge, are mechanisms for proving and preserving superiority. The very right to ask questions changes the level of relationship which may normally, as, with an examiner, be dominant or with a neurotic "parent," domineering.

Page 46:—Alice states that she looks like her father and talks like her mother.
Doctor's Comment: This confusion of identity is of importance in retarding maturation.
Reviewer: The word "maturation" is physiological. The doctor probably means "maturity" which is psychological. In any case, the lowest level of abstruction is the seeking of similarities, the next higher of differences and the highest of similarities of differences.

Page 47:—
Alice: I had great fear of my mother . . . of being hit, of being caught in a lie.
Doctor's Comment: Alice oscillating between her guilty fears at the age of six and her present code of conduct *in re* lying.
Reviewer: There are better and more mature reasons for telling the truth.

Page 56:—
Alice: When she said that my scratching affects my family she was right.
Doctor's Comment: Scratching . . . represents part of the total pattern of adaptation.
Reviewer: Verbatim recording abstracts from psychoanalysis, the projection of the analyst and the re-projection of the analysand. We are rid of psychological "Impressionism." The process matures the analyst who later, hearing his own words, discovers new overtones in his earlier statements.

Page 58:—
Alice: . . . my mother's favorite expression when she used to find my (bra) straps pinned was that I was a slob.
Reviewer: Patients in psychological turmoil often suffer anxiety because of false identification, confusing words and things.

Page 92:—
Mother: How can one go to one doctor for a whole year if you're not all healed?
Reviewer: The mother is unrealistic and immature. The patient goes at *intervals* over a *period* of a *year*. The mother seeks absolutes which do not exist as evidenced by "all healed."

Page 135:—
Doctor: How is she still punishing you?
Alice: By not talking and by being cool.
Reviewer: Punishment by ignoring, in other words, acting as though the other person did not exist is probably the most severe punishment available to human beings in their interpersonal relationships.

Page 185:—
Alice: When I became pregnant . . . I was afraid to tell my mother.
Doctor: The struggle for independence is still overshadowed by overwhelming childhood fears.
Reviewer: Dawning maturity, but not mature, for just so long as she shows more than realistic concern about *anybody's* reaction to anything that she does!

Page 201:—
Alice: And so, in not telling her everything it was a matter of avoiding more subterfuge and more lying.
Doctor: I don't see where there is lying. You gave her a limited version, didn't you?
Reviewer: The patient and the physician have not thought through the significance of lying as part of the maturing process.

Page 212:—Alice speaks of her recovery and of her changed relationships to her mother who has since died and to her husband with whom her relationship has improved. She can now integrate her new understanding into her daily life. The book ends with a discussion of the "Cronus Complex."

Not everybody will agree with the significance of the remarks made by Alice, the interpretations of the doctor and the asides of the reviewer. There will be the usual comment by mothers that their daughters are not "like that." There will be physicians (who as fathers or mothers) will be repelled on the same level and on another, as professionally, they learn that they must take into consideration the fact that verbatim reporting of psychoanalytical sessions must in this or some other form become part of their therapeutic techniques. To study one patient in depth takes practice. It is hard and often dull work. Let us be glad that an allergist trained in psychiatry has done it.

This book may be read with interest and profit by allergists and their patients.

THE NEW YORK ALLERGY SOCIETY

At the annual business meeting of The New York Allergy Society held November 28, 1956, the following officers were elected for the year 1956-1957: President, Samuel J. Prigal, M.D.; president-elect, Leoni N. Claman, M.D.; vice president, Samuel Bell, M.D.; secretary, Aaron D. Spielman, M.D.; treasurer, Joseph H. Fries; and assistant secretary-treasurer, Sheppard Siegal, M.D.

CONNECTICUT ALLERGY SOCIETY

The annual fall meeting of the Connecticut State Allergy Society was held at the Woodbridge Country Club, Woodbridge, Connecticut, November 8, 1956. The following officers were elected: President, Dr. George Hurwitz, Hartford; vice-president, Dr. Edward Vioni, Bridgeport; and secretary-treasurer, Dr. I. H. Krall, Hartford. The following were elected to the Executive Committee: Drs. Paul Winer, J. F. Beakey and Frederick Kessler.